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**Metal Template Synthesis of  
Hard-to-Access Mechanically  
Interlocked Molecules**

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Degree of Doctor of Philosophy

School of Chemistry

University of Edinburgh

*February 2013*

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*Dedicated to my Family*

謹獻給我最摯愛的家人

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## **Abstract and Layout of Thesis**

*The construction of mechanically interlocked molecules has been the subject of decades of research. The efficiency of strategies for preparing these molecules has increased continuously. In recent years, the transition metal templation strategy has played quite a remarkable role in the synthesis of entwined or mechanically bonded structures due to the metals' diverse coordination chemistry and ability to chelate ligands. In the early stages of this method's development, the metal ions were used as integral part of the scaffold for such components as rings and stoppers to generate the interlocked structures. In newly developed active metal templation strategies, metal ions are used to promote covalent bond forming reactions while simultaneously acting as structural supports.*

*In this thesis, three main aspects are expanded for the discussion of the application of metal template strategies. First of all, the newly developed strategy - active metal template - will be described and exemplified using the Huisgen-Meldal-Fokin Cu(I)-catalyzed 1,3-cycloaddition of azides with terminal alkynes (the CuAAC "click" reaction), the Cu(I)-mediated Cadiot-Chodkiewicz heterocoupling of an alkyne halide with a terminal alkyne, and the Ni(II)-catalyzed  $\text{Csp}^3\text{-Csp}^3$  homocoupling reaction.*


*Secondly, the thesis discusses the use of these strategies to obtain several hard-to-access structures, including the first high-yielding doubly threaded [3]rotaxanes, heterocircuit-catenanes and the one pot synthesis of homocircuit-catenanes, and the smallest molecular trefoil knot prepared to date.*

*Lastly, as an extension of the metal temptation strategy, the final chapter of this thesis will discuss the assembly of inorganic metal-organic catenanes by metal coordination.*

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## Declaration

The scientific work described in this thesis was carried out in the School of Chemistry at the University of Edinburgh between July 2008 and July 2011. Unless otherwise stated, it is the work of the author and has not been submitted in whole or in support of an application for another degree or qualification of this or any other University or institute of learning.

  
Signed.....

Date.....

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## Conferences and Meetings Attended

- 1. Organic Research Seminars**, University of Edinburgh, UK, 2008-2011.
  - a) *Active-Metal Template Synthesis of Catenanes*, November 2008.
  - b) *Active-Metal Template Synthesis of Catenanes and Knots* , October 2009.
  - c) *Active-Metal Template Synthesis of Hard-to-Access Mechanically Interlocked Molecules*, April 2011
- 2. School of Chemistry Visiting Speaker Colloquia**, School of Chemistry, University of Edinburgh, UK, 2008-2011.
- 3. SupraNano meeting**, University of Brighton, UK, 16/12, 2008. Poster entitled '*Active Metal Template Synthesis of Catenanes*'
- 4. 4<sup>th</sup> International Symposium on Macrocyclic and Supramolecular Chemistry**, Maastricht, The Netherlands, 21/06, 2009. Poster entitled '*Active Metal Template Synthesis of Catenanes*'
- 5. Scottish Chemical Industries Postgraduate Symposium**, University of St.Andrews, UK, 02/04, 2009.
- 6. International Conference of Coordination Chemistry**, Adelaide, Australia, 25/07, 2010. Oral presentation entitled '*Catalysis Using Macrocycle Bound Copper(I): Active Template Synthesis of [2]Catenanes*'
- 7. RSC Perkin Division 36th Scottish Regional Meeting**, University of Edinburgh, UK, 06/07. Poster entitled '*An Unusual Ni/Cu Bimetallic Active Template Reaction for the Synthesis of [2]Rotaxanes.*', 2<sup>nd</sup> Poster Award
- 8. Taiwanese Scientific Symposium**, University of Edinburgh, UK, 04/12, 2010 Oral presentation entitled '*Catalysis Using Macrocycle Bound Copper(I): Active Template Synthesis of [2]Catenanes*'
- 9. 6<sup>th</sup> International Symposium on Macrocyclic and Supramolecular Chemistry**, Brighton, UK, 07/07,2011. Poster entitled '*Active Metal Template Synthesis of Hard-to-Access Mechanically Interlocked Molecules*', Biomolecules and organics poster. Poster Award: 1<sup>st</sup>
- 10. 6<sup>th</sup> International Symposium on Advanced Challenges of Supramolecular Chemistry and Chemical Materials**, Beijing, China. 02/09, 2011. Poster entitled '*Active Metal Template Synthesis of Hard-to-Access Mechanically Interlocked Molecules*'

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The research described would not have been possible without the technical support I have received over the last three years, for which I would like to thank: Max, Bartek, Adam, Juraj, Miriam for keeping all things NMR and MS running smoothly; Alan Taylor, for a first class mass spectrometry service; Prof. Alexandra Slawin for solving crystal structures and Louise Hogg and Stewart Franklin for synthesizing some starting materials.

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Finally I would like to thank my family (especially for my beloved sister, Shan) for their support. Without them, I wouldn't have the courage to chase my dreams on another side of the world. The little girl always loves you.

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## List of Abbreviations

Ac	Acetyl
AMT	Active metal Template
APCI	Atmospheric pressure chemical ionization
Bipy	Bipyridine
b.p	Boiling point
br	Broad
Calcd.	Calculated
Cat.	Catalytic amount
CPK	Corey-Pauling-Koltun space filling model
CuAAC	Cu(I)-catalyzed Alkyne Azide 1,3-cycloaddition
d	doublet
DIPA	Diisopropylamine
DMAP	4-(Dimethylamino)pyridine
DME	Dimethoxyethane
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethyl sulfoxide
dpp	2,9-Diphenyl-1,10-phenanthroline
dppf	1,1'-Bis(diphenylphosphino)ferrocene
EDTA	Ethylenediamine tetraacetic acid
Equiv.	Equivalent
ESI	Electrospray Ionization



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FAB	Fast Atom Bombardment
H-bonding	Hydrogen bonding
HRMS	High Resolution Mass Spectrometry
<i>J</i>	Coupling constant
LRMS	Low Resolution Mass Spectrometry
MHz	Megahertz
mmol	Millimoles
M.p.	Melting point
MS	Mass Spectrometry
<i>m/z</i>	Mass-to-charge ratio
NHC	<i>N</i> -Heterocyclic Carbene
NMR	Nuclear Magnetic Resonance
ppm	Parts per million
Pybox	Pyridine 2,6-bisoxazoline
RCM	Ring Closing Metathesis
RT	Room Temperature
Sat.	Saturated
Terpy	Terpyridine
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TM	Transition Metal
TMEDA	Tetramethyl Ethylenediamine

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## General Comments on Experimental Data

Unless otherwise stated, all reagents were purchased from commercial sources and used without further purification. Dry dichloromethane was obtained by passing the solvent through an activated alumina column on a PureSolv<sup>TM</sup> solvent purification system (Innovative Technologies, Inc., MA). 6,6'-Dibromo-2,2'-bipyridine,<sup>1</sup> 2,6-bis(3-(4-hydroxyphenyl)-propyl)-pyridine,<sup>2</sup> toluene-4-sulfonic acid hex-5-ynyl ester<sup>3</sup> and toluene-4-sulfonic acid 6-azido-hexyl ester<sup>4</sup> were prepared following literature procedures. Petrol refers to the fraction of petroleum ether boiling in the range 40-60 °C. Flash column chromatography was carried out using Kieselgel C60 (Fisher) as the stationary phase, analytical TLC was performed on precoated silica gel plates (0.25 mm thick, 60F254, Merck, Germany) and observed under UV light. Preparative size exclusion chromatography was carried out using Bio-Rad S-X1 beads (40–80 µm bead size, 600–14,000 MW exclusion range) swollen in CH<sub>2</sub>Cl<sub>2</sub>. Preparative HPLC was performed on a Gilson Inc., USA instrument with a reversed-phase column (Ascentis® C18, 250 x 21.2 mm, 5 µm particle size, 15 mL/min flow rate). Microwave reactions were performed using a CEM Microwave Technology (Buckingham, UK) Discover apparatus, in Open Vessel mode and under one atmosphere of nitrogen. All <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on Bruker AV 400 or AV 500 (cryoprobe) instruments, at a constant temperature of 300 K. Chemical shifts are reported in parts per million and referenced to residual solvent. Coupling constants (*J*) are reported in hertz (Hz). Carbon NMR spectra were recorded as “PENDANT” experiments.<sup>5</sup> Assignment of the <sup>1</sup>H NMR signals was accomplished by two-dimensional NMR spectroscopy (COSY, TOCSY, NOESY, HSQC, HMBC). Standard abbreviations indicating multiplicity were used as follows: m = multiplet, quint. = quintet, q = quartet, t = triplet, d = doublet, s = singlet, br = broad, AB = AB quartet. All melting

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points were determined using a Sanyo Gallenkamp apparatus and are uncorrected. Low resolution MS analysis was performed on an Agilent Technologies 1200 LC system with 6130 single quadrupole MS detector (APCI or ESI source). High resolution ESI mass spectrometry was carried out by the EPSRC National Mass Spectrometry Service Centre (Swansea, UK). Ion mobility mass spectrometry measurements were performed on the MOQTOF, an in-house modified QToF 1 (Micromass UK Ltd).<sup>6</sup> The alterations involve the insertion of a 5.1 cm long copper drift cell and supplementary ion optics situated post source optics and before the quadrupole analyzer. A potential difference can be applied across the drift cell, thus when ions are pulsed into the drift cell (which is filled with helium gas) and drift through under the influence of this field, they are hindered by collisions with the intervening buffer gas molecules. Thus the time taken for ions to traverse the cell, in conjunction with the strength of the electric field applied across the drift cell, is due to the charge they carry and their mobility ( $K$ ).  $K$  is inversely related to the rotationally averaged CCS of the ion.

The ions then pass through the quadrupole and time of flight analyzers and are detected by microchannel plates. The time from when ions are pulsed into the drift cell to when they are detected is therefore a combination of the time the ions spend in the drift cell (drift time) and that outside it (dead time). This is obtained from the measured mass selected arrival time distribution (ATD), and can be deconvoluted into ATDs of each individual ion.

For a given mass/charge the drift time will vary depending on its CCS but the dead time will be invariant. The ions ATD distributions are measured to at least 6 different values of the electric field applied to the drift cell (drift voltage). If the arrival times are plotted

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against  $P/V$  the intercept will be the dead time and the gradient  $1/K$ . After normalizing for the experimental temperature and pressure inside the drift cell  $K$  can be converted into reduced mobility  $K_0$  and this to ascertain a value for  $\Omega$  using the equation below.

$$K_0 = \frac{3ze}{16N_0} \left( \frac{2\pi}{\mu k_B T} \right)^{\frac{1}{2}} \frac{1}{\Omega}$$

where  $z$  is ion charge,  $e$  is electron charge,  $N_0$  is the buffer gas number density,  $\mu$  is the reduced mass of the buffer gas and ion,  $k_B$  is the Boltzmann constant,  $T$  is the effective temperature and  $\Omega$  is the momentum transfer collision integral.

For IMMS a nano-electrospray (n-ESI) source was used for the introduction of samples into the mass spectrometer. Ions are produced by charging the solution by a platinum wire inserted into the capillary tip. This produces a plume of ionized droplets which are guided through the mass spectrometer down a voltage gradient. The n-ESI capillaries were prepared from glass capillaries (World Precision Instruments, Sarasota, USA) using a micropipette puller (Fleming/Brown P-97 Sutter Instruments, Novato, USA).

All three extended compounds were modeled in Spartan with a basic energy minimize function and the atomic coordinates submitted to MOBCAL software.<sup>7</sup> This allowed the CCS values of the three synthesized compounds to be calculated, implementing the trajectory method(TM).

# **Chapter 1**

## **Metal-Directed Synthesis of Mechanically Interlocked Molecules**

**Synopsis**

*A variety of mechanically interlocked molecules, such as rotaxanes and catenanes, have attracted chemists attention because of their complex and diverse structures and interesting potential application in material science. Since the first [2]catenane was synthesized in 1961, the development of high-yielding and efficient template synthetic routes has been one of the main areas in this field, challenging scientists to overcome the difficulties associated with manipulating molecular components in three-dimensional space. To date, metal ion template strategies have played an important role in the evolution of template synthesis of intertwined structures where transition metals orient the precursors into interlocked structures and link all components to form covalently trapped, kinetically stable molecules. This introduction chapter firstly outlines the concept and describes the key elements in this new methodology. Furthermore, the evolution of metal ion templation, significantly achievements and the future prospects will be summarized.*

**Acknowledgements:**

Thanks to Dr. Paul McGonigal and Chris Campbell for the fantastic proof-reading of this chapter.

## 1.1 Basics and Historical Background

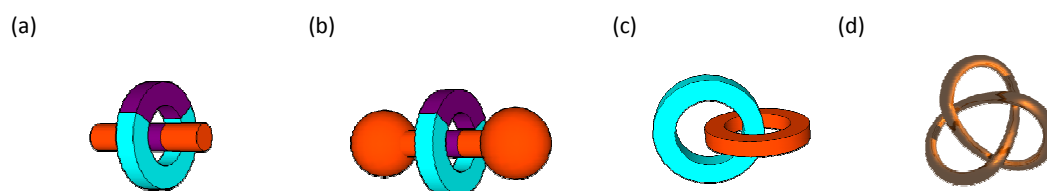
Over the last 60 years, the significance of mechanically interlocked molecules has increased because of their potential applications for catalysis, sensing, and molecular machines<sup>1</sup> as well as the recent discovery of many different natural DNA-catenanes.<sup>2,3</sup> Mechanically interlocked molecules are defined as structures in which two or more components are kinetically trapped together, often by virtue of manipulating non-covalent interactions, cross-over points and turns to form a complex architectures in which different components make up a single molecule that cannot be separated without breaking a covalent bond. Furthermore some proteins are also known to form molecular knots which, although, cannot technically be counted in the same class of interlocked molecules but do have a similarly complex in geometry.

### 1.1.1 Definitions and Nomenclature

To clarify what mechanically interlocked molecules are, firstly we have to know two basic structures in this class - rotaxanes and catenanes. Rotaxanes (from Latin *rota* meaning wheel and *axis* meaning axle) (Figure 1.1b), which contain a thread, a macrocycle ring and two stoppers are formed of a dumbbell shaped molecule threaded through one or more macrocycle rings. Related inclusion complexes (Figure 1.1a) in which the thread and the macrocycle are held together via non-covalent interactions are often known as *Pseudo*-rotaxanes. With a suitably sized dumbbell (stopper) which is bigger than the size of the cavity of the macrocyclic ring, the interlocked structure is then stable with respect to unthreading. Owing to their non-interlocked composition, therefore, pseudo-rotaxanes were not classified into the two basic groups of mechanically interlocked molecules.

Another example of interlocked molecules, catenanes (from Latin *catena* meaning chain) (Figure 1.1 c) consists of two or more interlocked macrocyclic rings. Normally, a numerical prefix is added as a descriptor to denote the number of components that are associated, e.g. a [3]catenane is made up of three linked macrocycles.

With the extension of the geometric complexity of some interlocked structures, more topologically complex entanglements and higher order links also play an important role in the application of mechanical bonded structures. The trefoil knot (Figure 1.1 d), for instance, is one example of the simplest knotted structure, bearing three crossing points within its structure, while [2]catenanes bears only two.



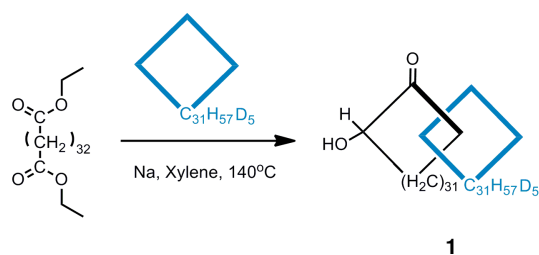
**Figure 1.1.** Schematic representations of a) a pseudo-rotaxane, b) a [2]rotaxane, c) a [2]catenane, (d) a trefoil knot

### 1.1.2 Early Syntheses of Interlocked Structures:

A number of different conceptual approaches toward the synthesis of catenanes were discussed by Lüttringhaus *et al.* in 1958.<sup>4</sup> A few years later, the first interlocked molecules, such as rotaxanes, were achieved by alternative synthetic routes.

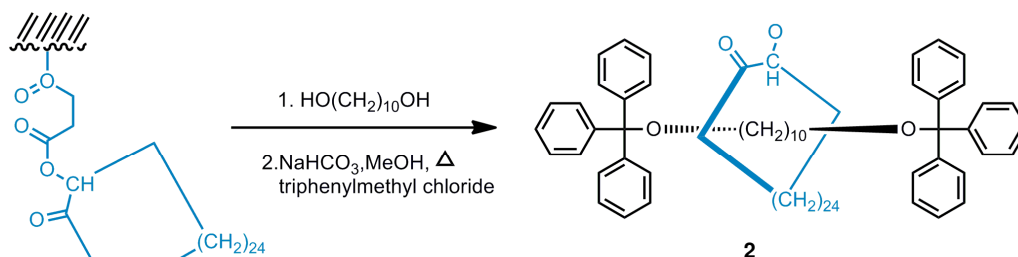
**Statistical strategies:** The method used for the first synthesis of interlocked structures is called the statistical approach<sup>5</sup> in which there is no guiding force to direct the interlocking. Therefore, all the successful examples rely on a very low random chance of a threading event. At the beginning of the 1960s, the first example of interlocked molecular rings was realized synthetically by Frisch and Wasserman. They performed a simple ring-closing reaction in a cycloalkane solvent, resulting in some of the rings closing around another ring (catenane). In Frisch's design, the cyclisation of a diethyl tetratriacontanedioate was used to form a cyclic acyloin, a yield of catenane **1** of less than 1% was thus obtained (Scheme 1.1).





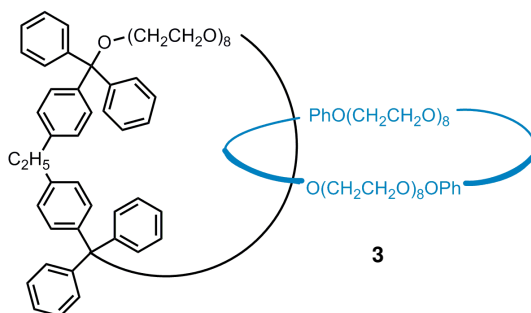
**Scheme 1.1.** Early examples of interlocked molecules

In 1967, the first synthesis of a [2]rotaxane **2** was reported by Harrison and Harrison in a 6% overall yield after repeatedly washing a resin bound macrocycle with thread components<sup>6</sup> giving what was called a “hooplane” at that time (Scheme 1.2).



**Scheme 1.2.** Early examples of interlocked molecules.<sup>7</sup>

Zilkha and Agam later published a more efficient statistical strategy which resulted in improved yields.<sup>7</sup> The results were reported in which statistical threading of a crown polyether by poly(ethylene glycol)400 leads to catenane **3** in 14% yield after cyclisation under high-dilution conditions (Figure 1.2).

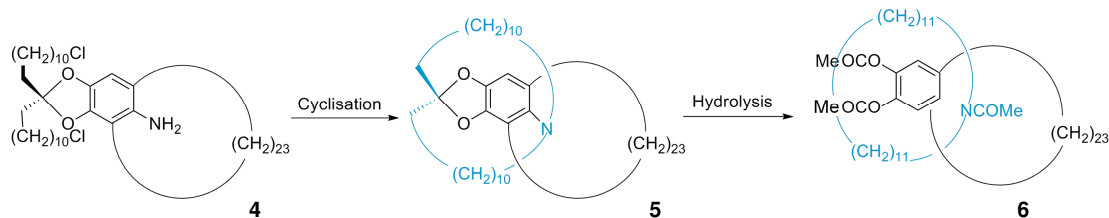


**Figure 1.2.** A catenane prepared from poly(ethylene glycol) and a mixture of dibenzo crown ethers.<sup>9</sup>

### 1.1.3 Template Directed Synthesis of Interlocked Architectures:

After further advances in research, two main general approaches emerged to efficiently yield rotaxanes or catenanes (apart from the 'statistical' method) - namely covalent bond template synthesis and non-covalent bond template.

**Covalent bond template synthesis:** In 1981, Schill and Lüttringhaus described the use of covalent bonds as a template for the first 'directed' synthesis of a mechanically interlocked molecule.<sup>5,8</sup> The synthetic pathway is shown in Scheme 1.4. In this multi-step synthesis, the aromatic amine **4** appears as a key intermediate which was cyclized to form the double ansa-compound **5**. Alkylation of the amino group occurs only when the two alkyl chloride chains are located above and below the plane of the central benzene ring to give **5**. Selective cleavage of the aryl-nitrogen bond and hydrolysis of the ketal group leads to [2]catenane **6**. Steric effects here control the cyclisation reaction decreasing the side reactions characteristic of the 'statistical' method.



**Scheme 1.4.** Schill's covalent bond-directed synthesis of a [2]catenane.

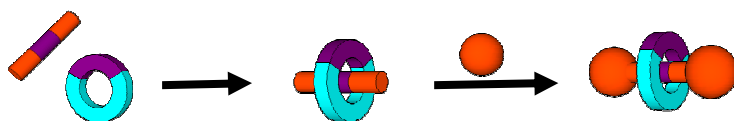
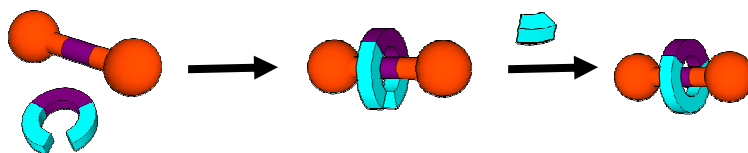
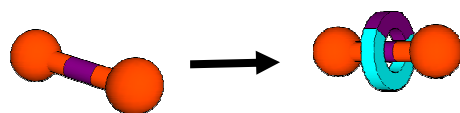
Schill's ingenious synthetic route illustrates the use of a covalent bond template to construct flexible mechanically interlocked architectures. However, such routes require many synthetic steps and a high level of technical expertise and thus limited the study of interlocked compounds.

**Non-covalent bond templates:** The formation of stable interlocked systems in high yields was achieved by exploiting non-covalent, weak intermolecular interactions from the early 1980s. Over the past thirty years, various and diverse recognition

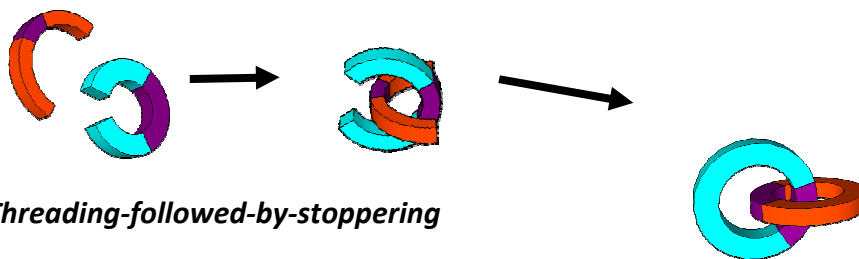
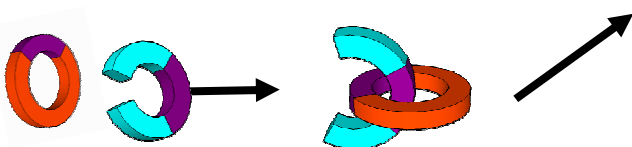
motifs such as hydrogen bonds<sup>9</sup>, metal coordination<sup>10</sup>, and donor-acceptor  $\pi$ -stacking systems<sup>11</sup>, have been used as a back bone for the synthesis of complex interlocked architectures.

This template directed strategy was an enormous leap forward. The work of Sauvage achieved higher yields of interlocked structures by controlling the orientation of ligands around a metal centre.<sup>12</sup> Two template effects, thermodynamic and kinetic effect were also studied and both of them were used to drive the synthesis and achieve higher yields in comparison with the statistical method. In examples employing a thermodynamic template effect (or equilibrium template), one product is impounded by the metal ion from a dynamic, equilibrating reaction mixture. Thus, the composition will be driven towards the product through Le Chatelier's principle. The kinetic effect is said to be acting when ligand geometry, controlled by the metal ion, dictates the outcome of the reaction – the major product is determined by the most favored conformation of an intermediate. Metal ion template effects have subsequently been used to access many macrocyclic and cage structures and continue to be explored in many areas of synthesis.<sup>13</sup>

The protocols for formation of interlocked molecules is illustrated for a simple [2]rotaxane (Figure 1.3). **The capping method** allows the synthesis of rotaxanes by covalent attachment of two bulky stoppers to both termini of the linear thread of a pseudorotaxane (also known as a stoppering reaction). Conversely, in **the clipping strategy** a macrocyclic ring is assembled around a preformed dumbbell. Williamson ether synthesis has been widely utilized to link the termini of a linear macrocycle precursor to form the interlocked structure in the metal ion template synthesis of catenanes and rotaxanes. **The slipping protocol** involves threading dumbbell shape molecules through a preformed macrocycle at elevated temperature followed by subsequent cooling to kinetically trap the rotaxane architecture.

**(i) Capping (Threading-followed-by-stoppering)****(ii) Clipping****(iii) Slipping****Figure 1.3.** Strategies for the template assembly of [2]rotaxanes.

The template strategies applied in the synthesis of catenanes are similar but slightly different since the target products contain two fixed rings. A ring closing reaction is necessary even in the stoppering technique where one ring is already preformed.

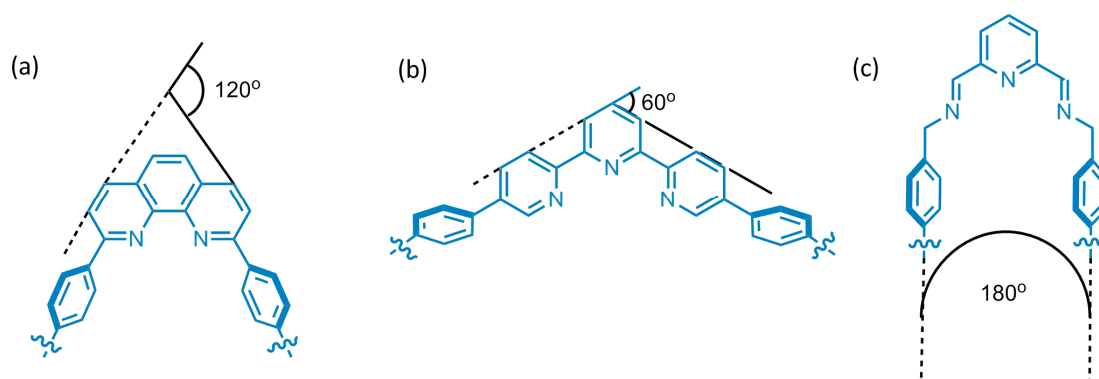
**(i) Clipping****(ii) Threading-followed-by-stoppering****Figure 1.4.** Strategies for the template assembly of catenanes.

## 1.2 Towards a Mechanically Bonded Structure

An analogy for the formation of interlocked molecules is that statistical methods are like trying to thread a needle by throwing a ball of string from other side of the room, so that very poor yields are obtained by this method. Directed synthesis, however, is like trying to thread a tiny needle by hand, a laborious, time consuming task. Therefore, 6–20 step synthetic routes were necessary; ending up with less than 1% overall yield. For metal template strategies, it could be imagined that the needle wants to thread itself due to a thermodynamic template effect. Therefore, these protocols provide access to interlocked molecules via high yielding, shorter syntheses and can be viewed as a great advance in comparison to the early-stage synthetic routes.

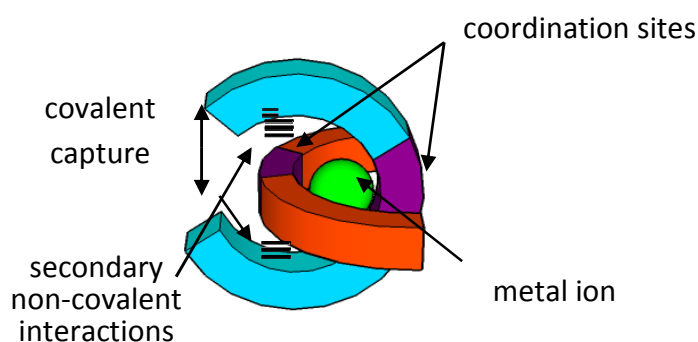
### 1.2.1 Key Components in Metal Templatation Tactics

When designing a prospective metal template synthesis of an interlocked structure, **turns, cross-over points and threadings** are the three main factors which should be considered. **Molecular turns** can be created by geometrically constrained ligands, such as rigid polycyclic ring systems; this creates a three dimensional structure which is suitably predisposed to mechanical bond formation. In other traditional non-metal templatation strategies, ion-pairs, partial charge complementarities, or hydrogen bonding partners have been utilized in the design of molecular turns.<sup>14</sup> Figure 1.5 shows different turn angles that can be induced by different ligand designs.



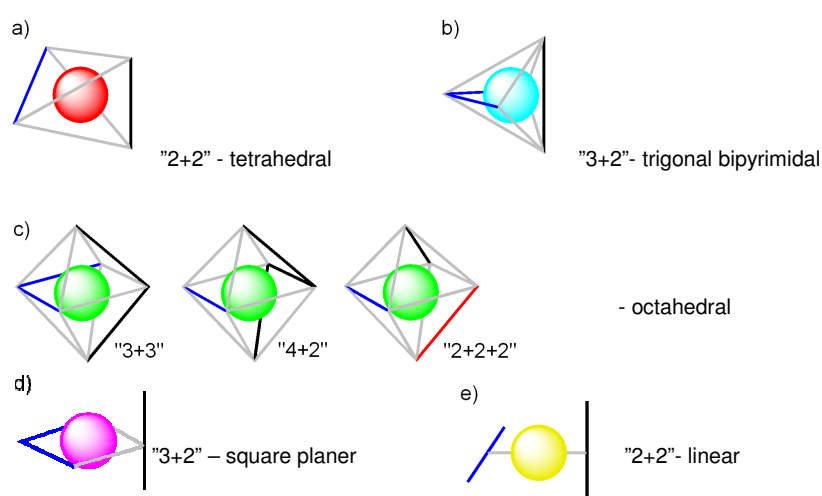
**Figure 1.5** Three examples of N-donor ligands that create different turn angles around a metal ion template. a) phenanthroline ligand units generate a 120° turn; b) terpyridine ligands generate a 60° turn and c) 2, 6-disubstituted pyridine ligands generate a 180° turns.

**Cross-over points** are created between different ligand sites (with appropriate molecular turns) by transition metal ‘anchors’ before the interlocked structure is covalently captured. The topology of the interlocked architecture can be varied by the use of different turn angles and various numbers of cross-over points. To orient the ligands to be able to overlap physically and to spontaneously create the cross-over point, the coordination geometry of the metal ion is the first important factor to be considered. (Figure 1.6)



**Figure 1.6** The use of secondary non-covalent interactions between two ligands could aid the orientation of the ligands (turn angle).

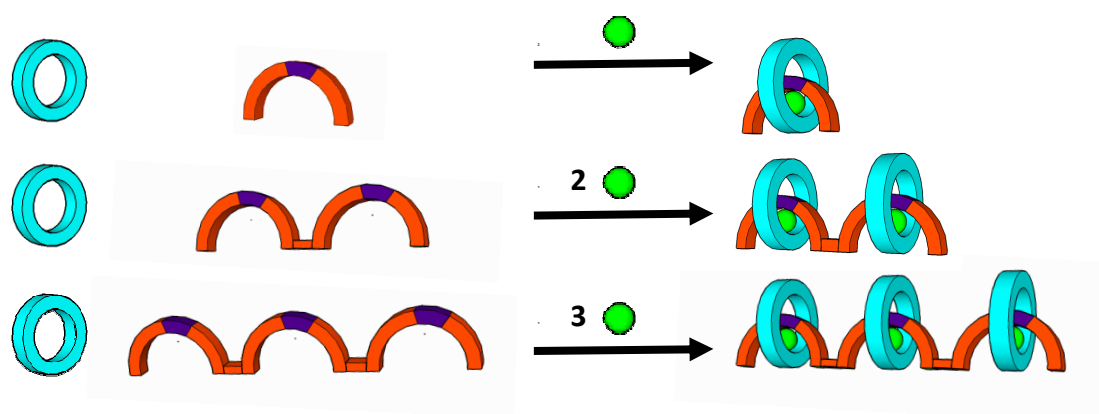
In addition a thermodynamically stable complex between ligand and metal is desirable. Figure 1.7 shows some examples of metal geometries which have been widely utilized to construct various interlocked structures by the coordination geometry of metal-ligands. As shown from the figure, two dimensional orientations could be arranged by square planar metal-ligand coordination geometry (Figure 1.7d) and linear template (Figure 1.7e), whilst three dimensional crossing-points could be generated by either an octahedral or a tetrahedral geometry. (Figure 1.7 a, b, c).



**Figure 1.7** The geometry of coordination number 2(e), 4(a, d), 5(b), 6(c), donor ligand sets could be used to construct and form the mechanically interlocked molecules.

A large amount of research has been carried out to determine the geometries of metal-ligand complexes.<sup>15</sup> However, it was well-known that it is more efficient to form homoleptic complexes with ligands which possess the same number of donor atoms as coordination sites on metal ion. For example, in the three dimensional categories of '2+2''3+3' donor sets; Cu(I), Fe(II) and Co(III) have been largely utilized to assemble stable mechanically interlocked molecules via chelation with a variety of ligands. Cu(I), for example, has widely been used with a (2+2) donor set in which its tetrahedral coordination geometry is able to template and form the simple two crossing-point, by chelating with two bidentate ligands, necessary for a catenane.<sup>16</sup>

The third component, **molecular threadings**, are commonly used in chemical templation strategy for higher order or oligomeric interlocked structures in which linear thread is placed through a macrocyclic component. These units can be connected, without loss of crossing points to generate multiply threaded molecules. This strategy is efficient for synthesizing higher order structures or delicate motifs, and could also be extended to form the poly-interlocked structures when multiple turns and several cross-points were linked.<sup>17</sup> (Figure 1.8)

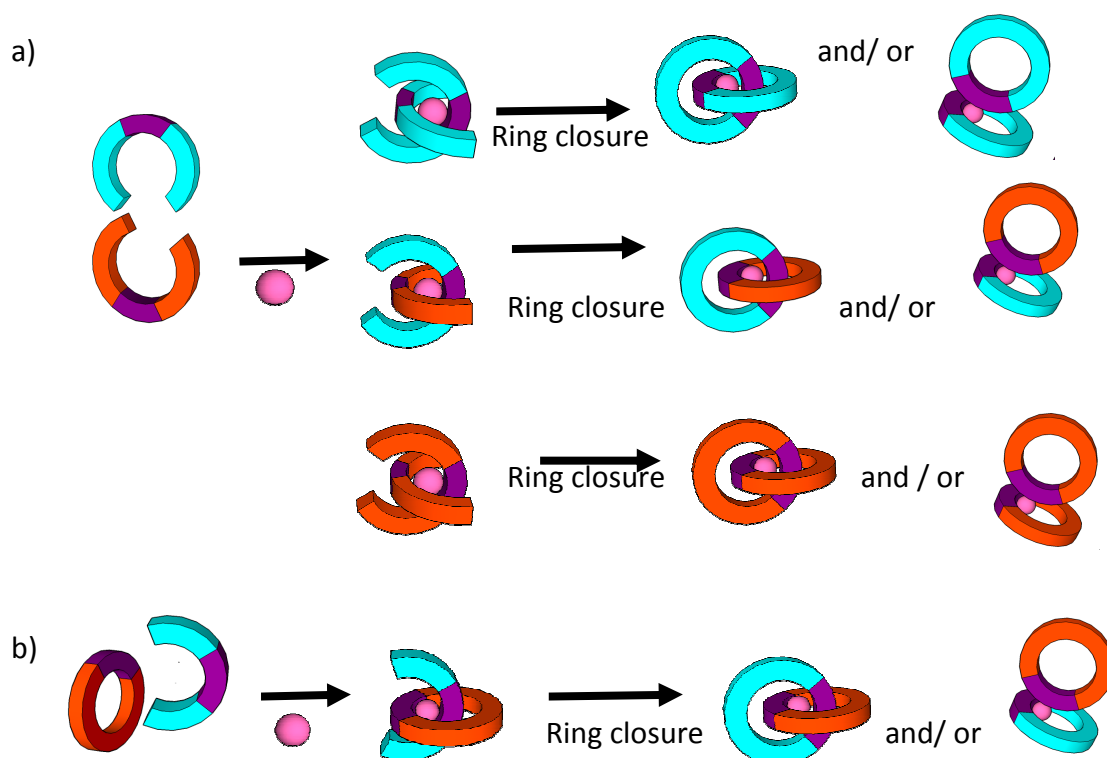


**Figure1.8** Molecular threading could generate the higher order structures by connection of a larger numbers of threads.

### 1.2.2 Actions Toward Mechanical Bonds

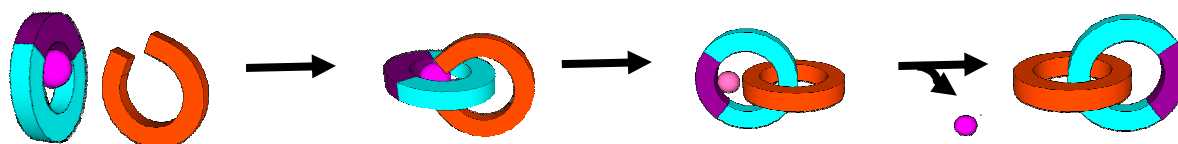
Once the three main factors of turns, cross-over points and threadings are appropriately gathered and well-located, the tactical formation of mechanical bonds is another issue. Even with the presence of the metal-ligand template, unfavorable non-interlocked structures, oligomers and polymers, can still be obtained as undesirable side products. In order to reduce the yields of side products and to promote the formation of the interlocked structures metal catalyzed covalent capture strategies have generally been used as an efficient way of ring closure. Various reactions have been reported to accomplish this mechanical bond formation.<sup>18</sup> (Figure 1.9)





**Figure 1.9.** Strategies for the template assembly of mechanically interlocked molecules

Recently, **the active-metal template strategy** has begun to be explored by the Leigh and Saito research groups.<sup>19</sup> In this strategy, metal ions catalyze covalent bond formation while simultaneously acting as a template for the assembly of the mechanically interlocked structure. This thesis will discuss in detail the recent developments and application of this new method in the following chapters. (Figure 1.10)

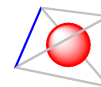


**Figure 1.10.** Active metal template strategy of [2]catenanes.

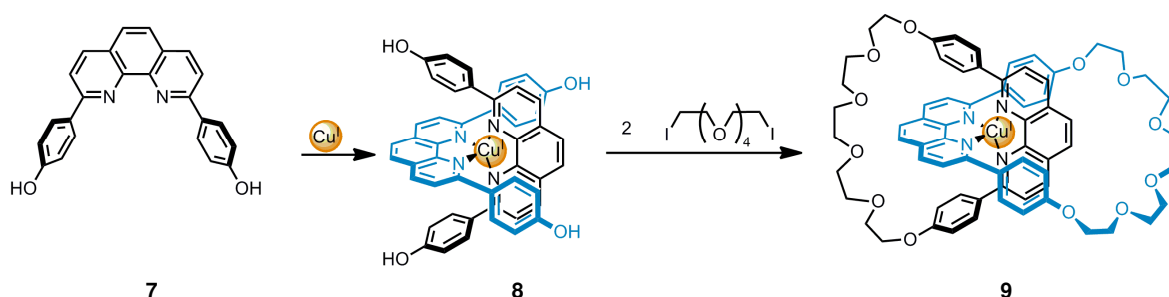
## 1.3 Comparison of Metal Templates

### 1.3.1 Passive Metal Templates

#### 1.3.1.1 Sauvage's Achievement: Tetrahedral Metal Templates '2+2':

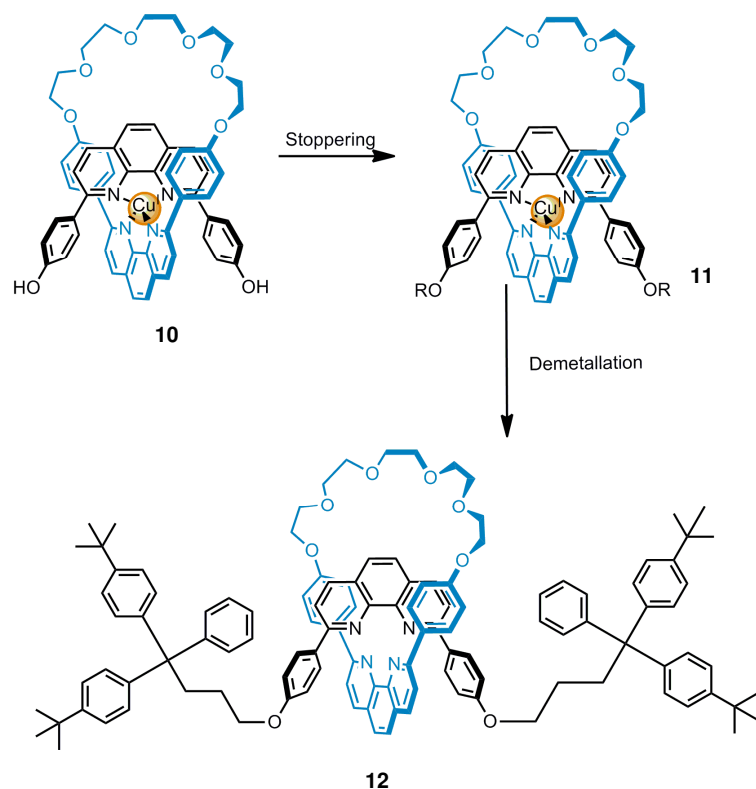


In 1983, the Sauvage group successfully turned interlocked architectures from chemical curiosities into readily accessible molecules by performing the first metal templated synthesis of a [2]catenane **9**.<sup>20</sup> This seminal work utilized the ability of transition metals to predispose ligands in a predictable spatial orientation to create cross-over points that directed subsequent macrocyclisation reactions towards interlocked products. The preferred tetrahedral geometry of Cu(I) was employed to organize two bidentate phenanthroline ligands **7** in a mutually orthogonal manner (Scheme 1.5).<sup>21,22,23</sup>



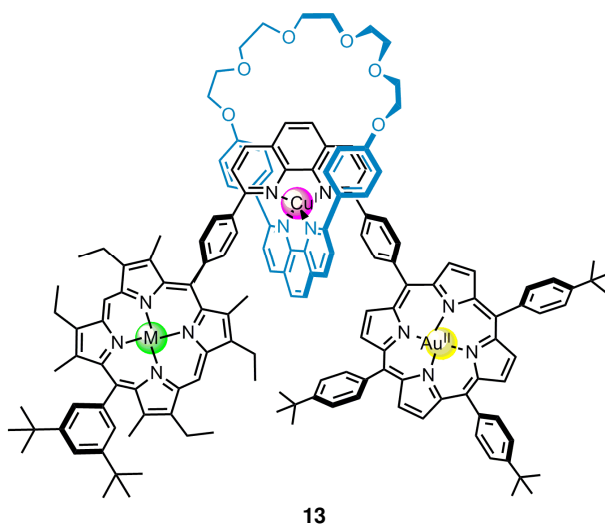
**Scheme 1.5.** Sauvage's metal template bond-directed synthesis of a [2]catenane.

This original strategy was then developed by the Gibson group to form [2]rotaxane **12** via a 'threading-followed-by-stoppering' approach where pseudorotaxane complex **11** was prepared, which followed by Williamson reactions with bulky stoppering groups gave the rotaxane product (Scheme 1.6).



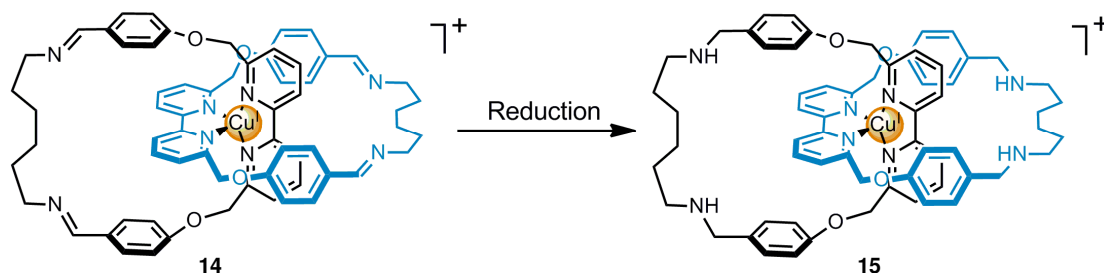
**Scheme 1.6.** Gibson's original Cu(I) directed [2]catenate synthesis.

Sauvage also prepared [2]rotaxane **13** via a similar 'threading-followed-by-stoppering' approach using porphyrin formation as the stoppering reaction and studied photo-induced electron transfer between the metallated porphyrins.<sup>24</sup> (Figure 1.11)



**Figure 1.11.** Sauvage's porphyrin rotaxanes with three metal ions.

Lindoy and co-workers developed an alternative approach by the use of the reversible imine formation with a Cu<sup>I</sup> bis-bpy core. (Scheme 1.7) Investigating the X-ray structure of **15** it was found that the two binding motifs are close to the ideal orthogonal geometry and the Cu(I) center is almost perfectly tetrahedral.<sup>25</sup>



**Scheme 1.7.** Lindoy's imine formation with Cu(I) bis-bpy ligand donor set.

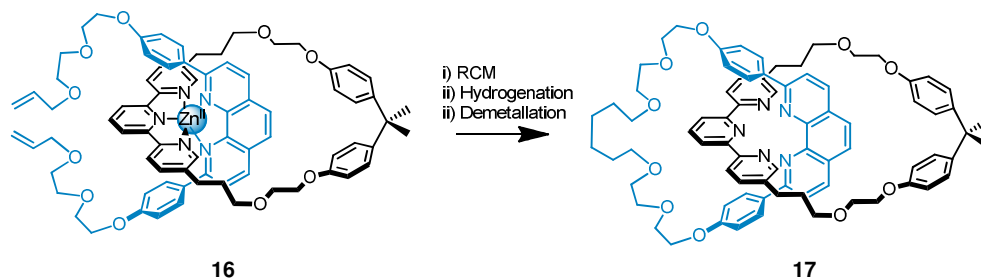
Some higher order structures have also been achieved by using this coordination geometry<sup>26</sup>, the Sauvage group, for instance, utilized the linking of pseudorotaxanes to form [ $\geq 3$ ]catenanes<sup>27</sup>, [ $\geq 3$ ]rotaxanes and knots which could be accessed by using either Williamson ether synthesis or oxidative acetylene coupling reactions and later by RCM.<sup>28</sup> Kim's group also used a similar approach to form a [5]catenane 'molecular necklace' from threaded cucurbituril macrocycles and Pt<sup>II</sup>(en) connecting units.<sup>29</sup>

### 1.3.1.2 Trigonal Bipyrimidal Metal Templates '3+2'



In contrast to the '2+2' tetrahedral, the trigonal bipyrimidal donor set must use two non-identical ligands to assemble a five-coordinate metal complex. Sauvage, used a tridentate (tpy) and a bidentate (dpp) ligand to introduce a turn about a five-coordinate metal ion. Forming pseudo rotaxane complex **16** followed by ring closing metathesis could afford the pentacoordinate Zn catenane **17**. (Scheme 1.8). The metal ion used in this strategy was Zn(II)<sup>30</sup> however the metal free catenand **17** was

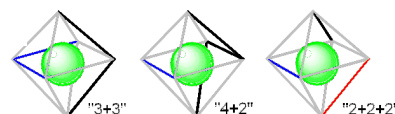
found to be able to bind both Cu(II) or Fe(II)<sup>34</sup> consequently generating by chelating of a bidentate dpp-based unit from a tripyridyl(tpy)-based macrocycle.



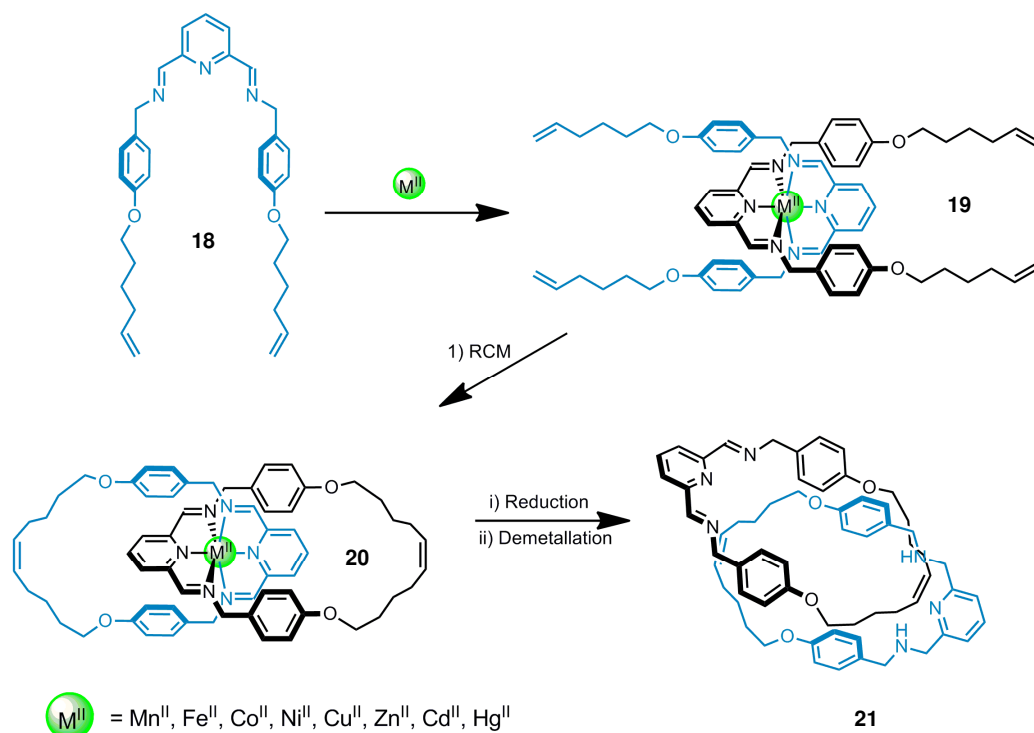
**Scheme 1.8.** Sauvage's assembly of catenane by utilizing zinc(II) as the trigonal bipyramidal geometry donor-ligand set.

The Sanders' group used two penta-coordinated Lithium ions to guide the interlocking when the components have assembled predominantly by pi-pi stacking<sup>31</sup>

### 1.3.1.3 Octahedral Metal Templates '3+3', '4+2', '2+2+2'



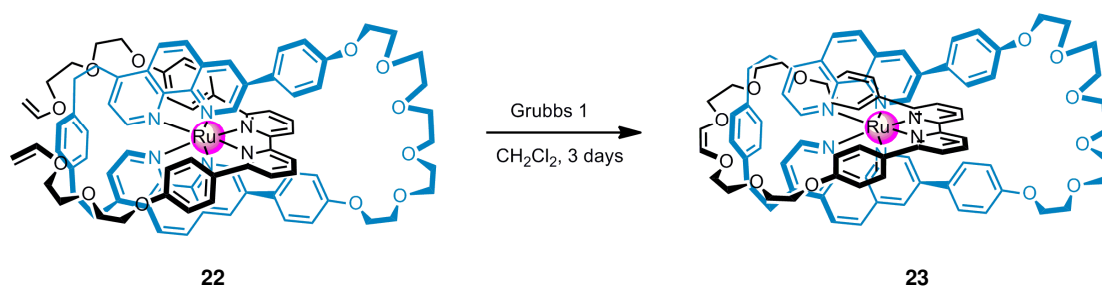
'3+3' donor ligand sets are a similar strategy to the '2+2' donor set. In this category, the Sauvage groups and Siegel groups utilized Ru(II)<sup>32</sup>, Fe(II)<sup>33,36</sup> and Co(II)<sup>35</sup> ions coordinated to two terpyridine ligand which could afford the desired interlocked structure.<sup>34</sup> Various divalent octahedral metal ions have been used to assemble interlocked structures in good yield incorporating modified 2, 6 diiminopyridine motifs<sup>35</sup> (Scheme 1.9).



**Scheme 1.9.** The assembly of a [2]catenane by the use of various octahedral geometries metal complexes.

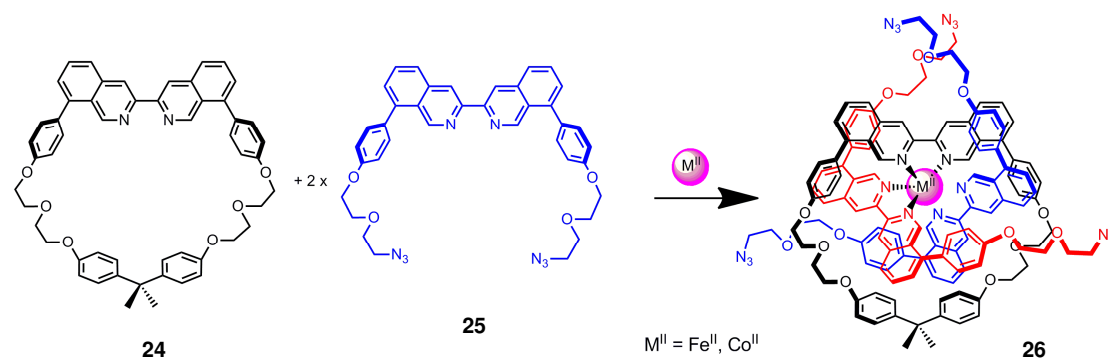
A similarly efficient strategy used imine bond forming reaction in conjunction with metal ion templation to place a thread through a bis-imine macrocycle ligand successfully obtaining rotaxanes in high yields. This method could be further extended to use harder trivalent metal ions such as cobalt(III).<sup>36</sup>

**'4+2' Donor ligand set** utilized a preformed tetradentate macrocycle with a Ru(II) metal complex.<sup>37</sup> (Scheme 1.10)



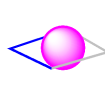
**Scheme 1.10.** '4+2' Donor ligand set utilized a preformed tetradentate macrocycle with a Ru(II) metal complex

A '**2+2+2**' donor ligand set was also utilized with an octahedral geometry metal ion for forming a triply entwined complex. Fe(II) or Co(II) coordinated to preformed isoquinoline macrocycle **24**, followed by chelation with two biisoquinoline ligand building blocks **25** to generate pseudorotaxane **26**.<sup>38</sup> Different donor ligand sets for octahedral metal ions were also investigated.<sup>39</sup> (Scheme 1.11)

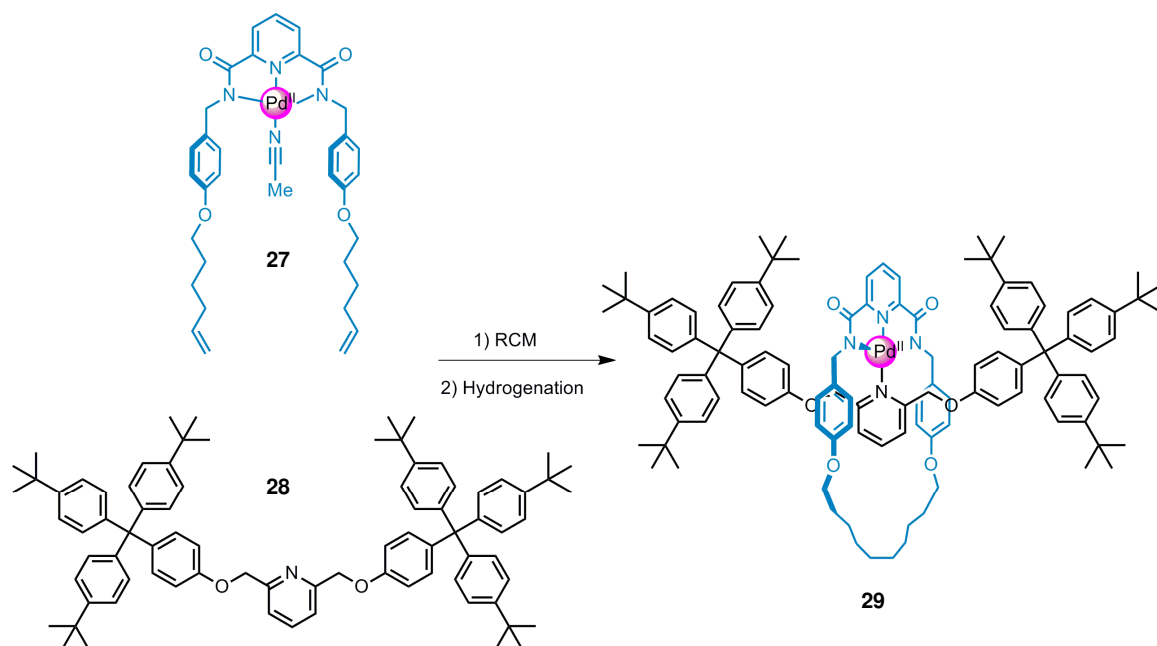


**Scheme 1.11** Two biisoquinoline ligand building blocks **25**, along with macrocycle **24** from which an octahedral metal ion containing pseudorotaxane **26** could be generated.

#### 1.3.1.4 Square Planer Metal Templates : '3+1'

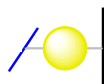


A Pd(II) metal complex, with its square planar coordination geometry, was successfully developed utilizing the '3+1' donor ligand set for the formation of interlocked structures. A preformed Pd(II) complex with the tridentate ligand pyridine 2,6-dicarboxamide **27** was added to of the monodentate pyridine thread **28**, containing bulky stoppers. Rotaxane **29** was thus obtained after RCM. A related catenane was also generated with the same basic ligand structure.<sup>40</sup> (Scheme 1.12)



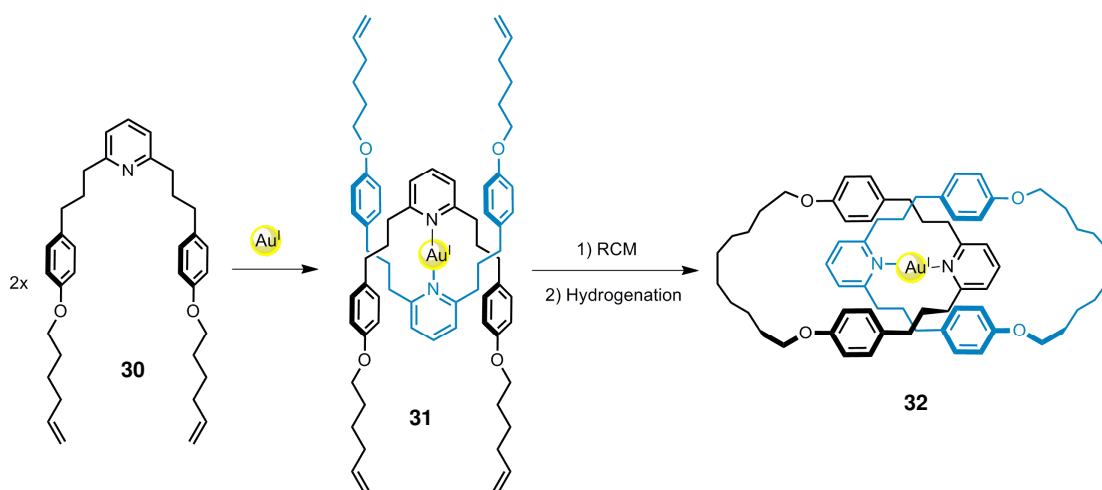
**Scheme 1.12.** The Pd(II)/tridentate ligand complex **27** was combined with monodentate pyridine thread **28** having bulky stoppers, rotaxane **29** was then obtained via RCM.

### 1.3.1.5 Linear Metal Templates: '1+1'



A '1+1' donor ligand set which utilizes two monodentate ligands coordinated to a one dimensional metal ion such as Au(I) has been proven to be a viable template for the generation of [2]catenanes.<sup>41</sup> The X-ray crystal structure demonstrates the linear pyridine-Au(I)-pyridine coordination geometry. Scheme 1.13 shows a [2]catenane **32** could also be assembled via a statistical Au(I) complex with suitable ligands.



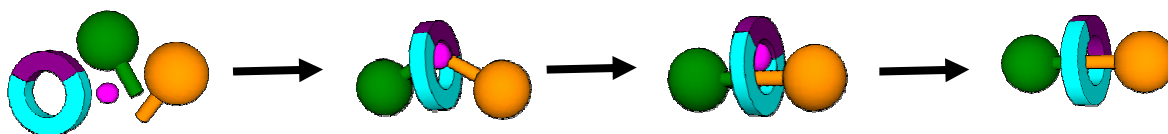


**Scheme 1.13.** '1+1' donor ligand set example using a pyridine-Au(I)-pyridine coordination.

### 1.3.2 Active Metal Templates (AMT)

#### 1.3.2.1 The Concept of an Active Metal Templates

In contrast to the passive templates, discussed above, transition metal ions in active metal template strategies play a dual role: Acting as both as a template for guiding and entwining or threading the components and also to act as a catalyst to promote the covalent capturing the interlocked products.<sup>42</sup>(Figure 1.12)

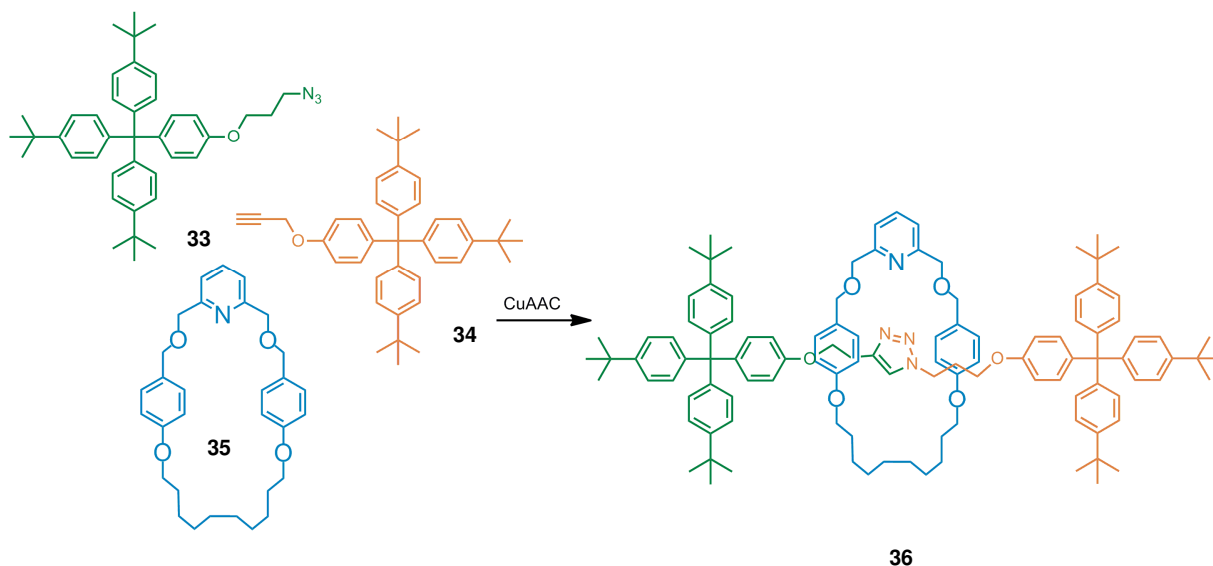


**Figure 1.12.** Active Metal Template strategy to synthesize [2]rotaxanes.

#### 1.3.2.2 Cu(I)-catalyzed AMT Reactions

The first AMT synthesis reaction was reported in 2006, using a copper-catalyzed cycloaddition reaction generating rotaxanes in near quantitative yields.<sup>43</sup>(Scheme 1.14) A preformed macrocycle with either monodentate **35** or bidentate ligand motif

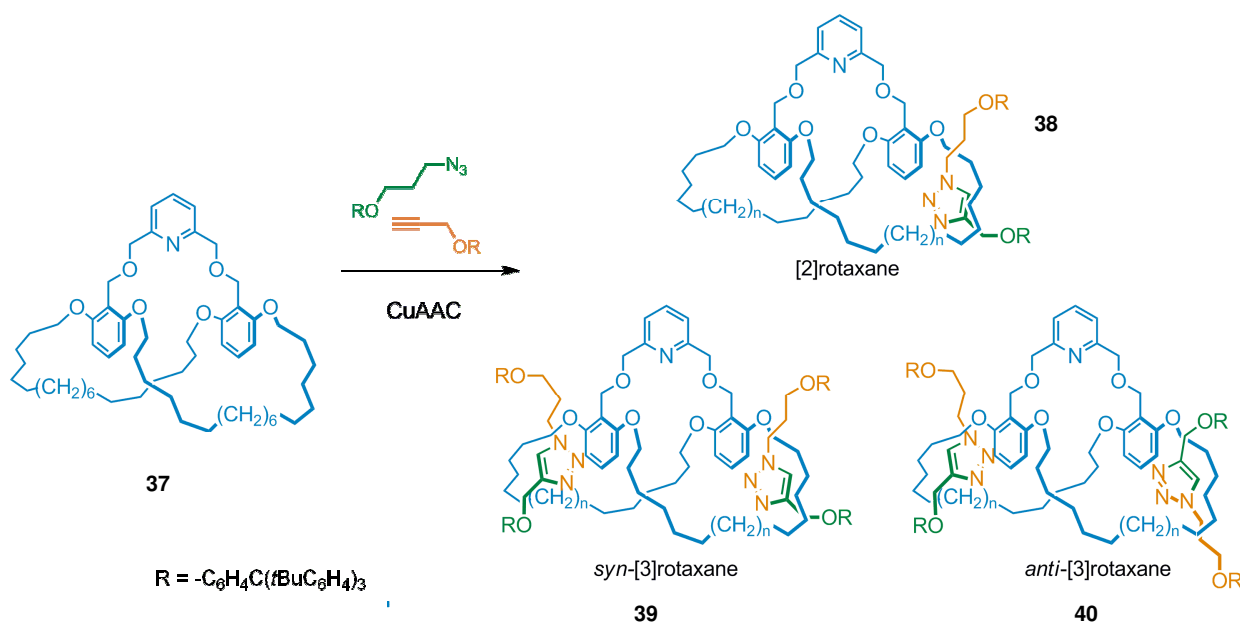
could be used. The mechanism involves two functionalized stoppers, one with a terminal azide **33** which reacts with alkyne terminal stopper **34** via Cu(I) catalyzed cycloaddition within the cavity of macrocycle **35**. One axle with two macrocycles, a [3]rotaxane **36** was also unexpectedly obtained under certain conditions indicating the proposed mechanism undergoes via a bi-metal ion intermediate.<sup>44</sup>



**Scheme 1.14.** A copper-catalyzed cycloaddition reaction could generate the rotaxane in near quantitative yields.

Active metal template synthesis of [2]catenanes via CuAAC could also be achieved.<sup>45</sup> Using a pyridine ligand macrocycle afforded heterocircuit [2]catenanes, whilst a more efficient one pot process generated homocircuit [2]catenanes by using a suitable monodentate pyridine ligand building block via double macrocyclization. More details about the synthesis of [2]catenanes will be discussed in Chapter 3 of this thesis.

Furthermore, doubly threaded rotaxanes were achieved when macrobicyclic ligand **37** with a monodentate was utilized as a reagent. The strategy could successfully applied to Cu(I)-catalyzed azide-alkyne cycloaddition (the CuAAC reaction) in a one pot synthesis. The doubly threaded [3]rotaxane (**39+40**) with two identical axles could be generated.(Scheme 1.15)

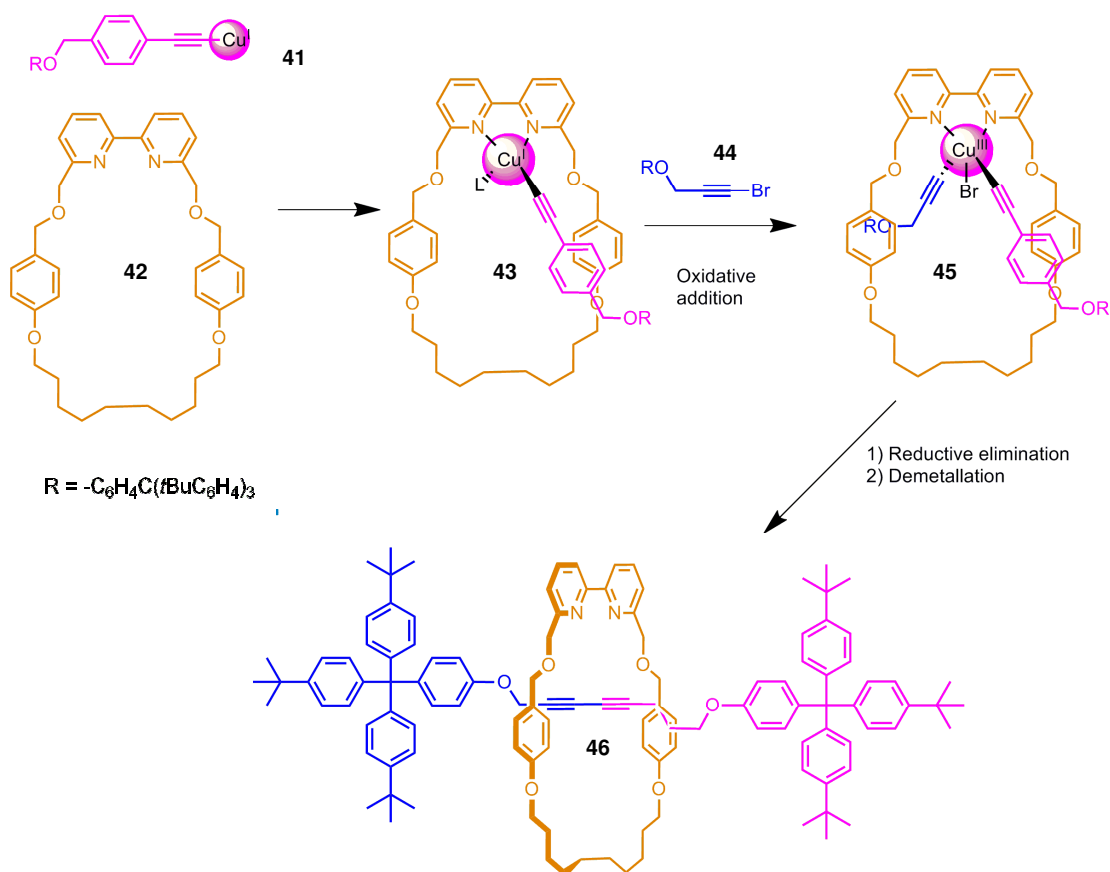


**Scheme 1.15.** Doubly threaded rotaxanes by assembly of the macrobicyclic [3]rotaxane, with two thread.

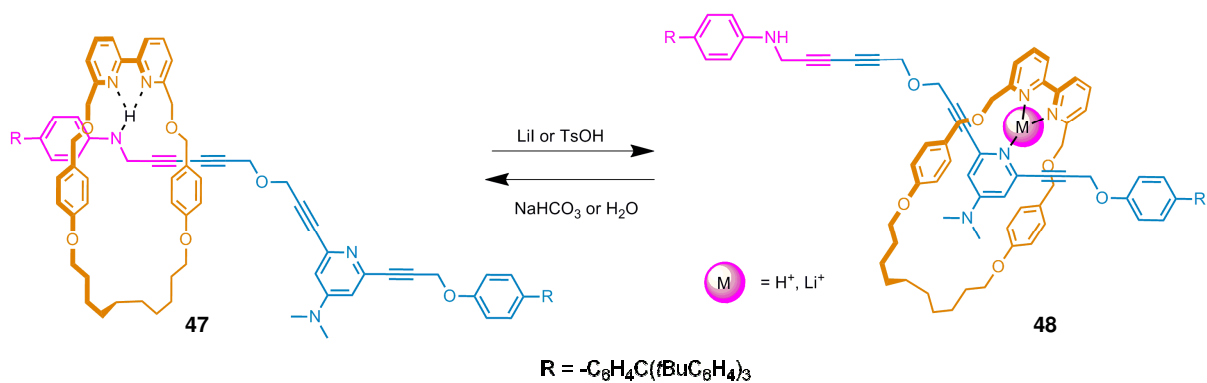
### 1.3.2.3 Metal-catalyzed Alkyne Alkyne Coupling AMT Reactions

Alkyne alkyne coupling reactions catalyzed by a Cu(I) complex (Glaser reaction) afforded symmetrical interlocked molecules. A preformed dpp-based macrocycle and two equivalents of alkyne terminal stoppers generated bis-alkyne rotaxanes. This method was later applied to the synthesis of [2]catenanes.<sup>46</sup>

Unsymmetrical rotaxanes via heterocoupling reactions could be achieved by using the Cadiot-Chodkiewicz Cu(I) catalyzed reaction. The acetylene stopper is transformed to the cuprate complex **41** in the first step, followed by coordination with bi-pyridine macrocycle **42**, the halo-alkyne terminal stopper **45** is then added into the solution and via a the heterocoupling reaction the [2] rotaxane **46** is formed.(Scheme 1.16)



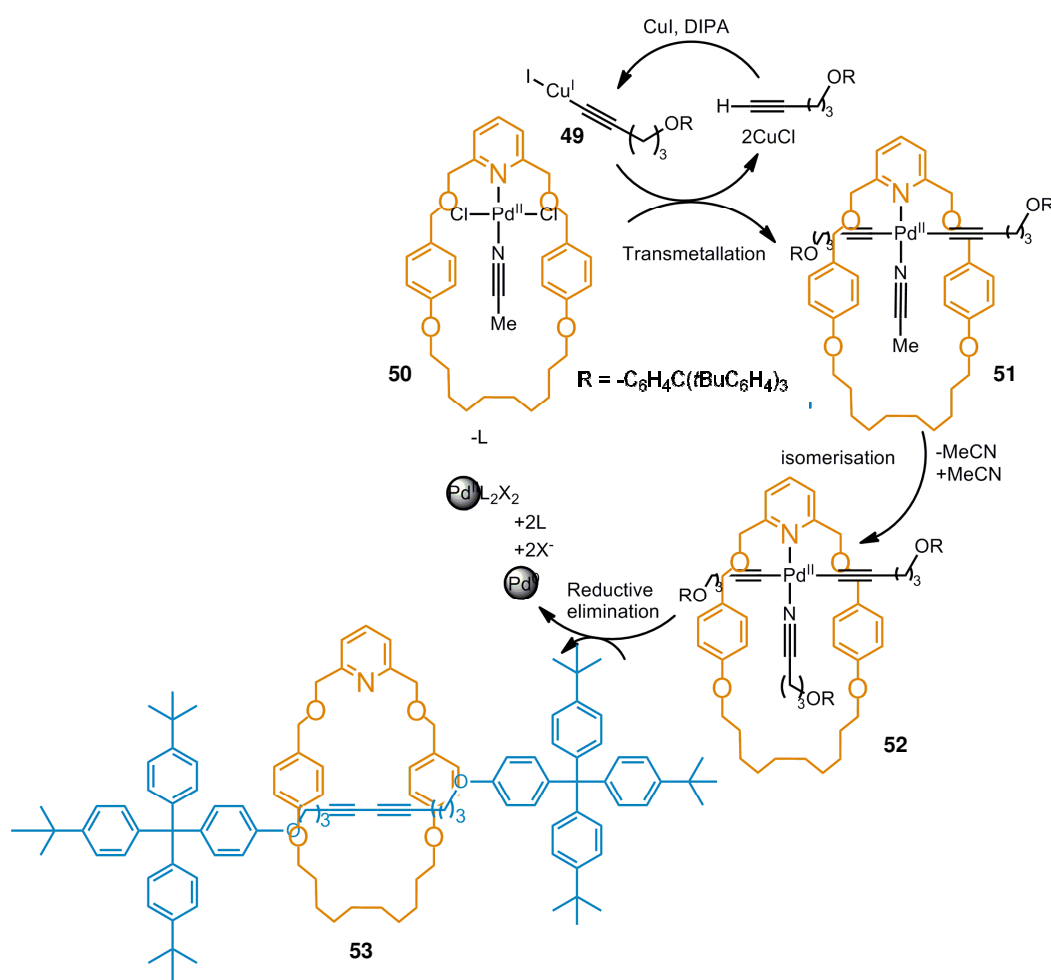
**Scheme 1.16.** Cadiot-Chodkiewicz Cu(I) active template synthesis of [2]rotaxane.



**Scheme 1.17** A molecular shuttle synthesised by the Cadiot-Chodkiewicz Cu(I) active template strategy. The position of the macrocycle on the axle could be switched by adding TsOH or lithium iodide. Adding base or water could drive the macrocycle back to the original position

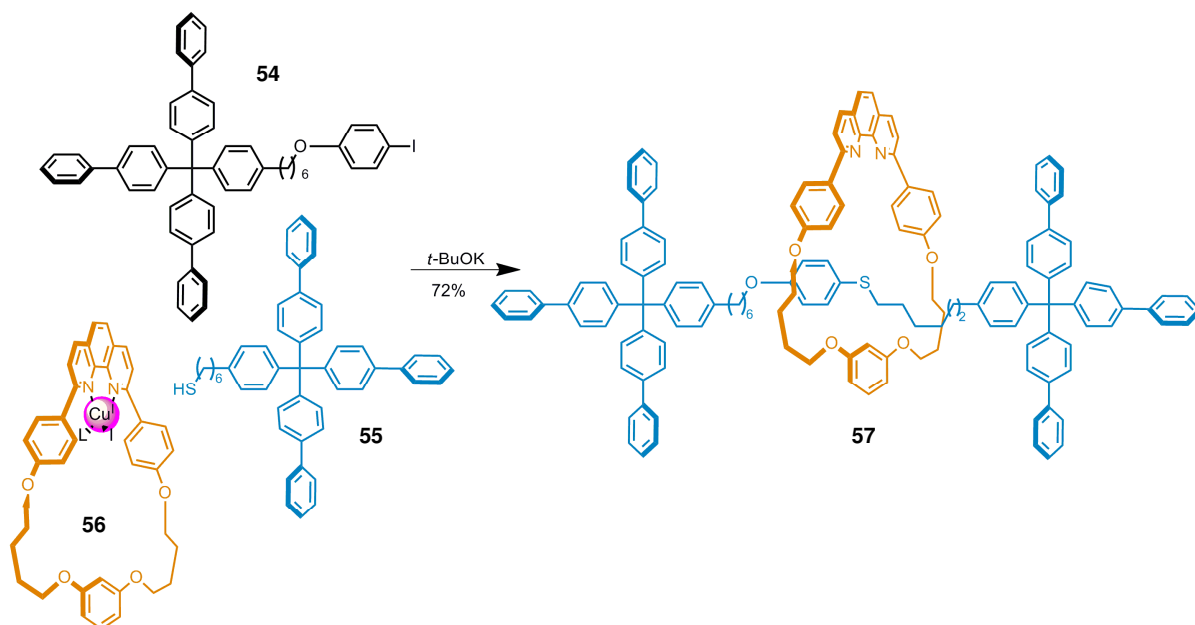
A switchable rotaxane-based molecular shuttle could be assembled utilizing the features of this reaction, that is, the recognition sites of the reagents do not persist in the products. A molecular shuttle **47** with weak intercomponent interactions could be synthesised by an active template Cadiot-Chodkiewicz reaction. The position of the macrocycle on the axle could be switched between the two weakly binding recognition sites using different reaction conditions. (Scheme 1.17)

Alkyne-alkyne bond formation could also be applied to AMT synthesis by the use of Pd(II) as the catalyst.<sup>47</sup> Copper-acetylide **49** was prepared with a functionalised alkyne stopper. After transmetallation by Pd(II), the ligands do not detach from the metal ion centre and hence the threaded geometry is maintained. Reductive elimination follows and the C-C bond is formed giving [2]rotaxane **53** in up to 90% yield. (Scheme 1.18)



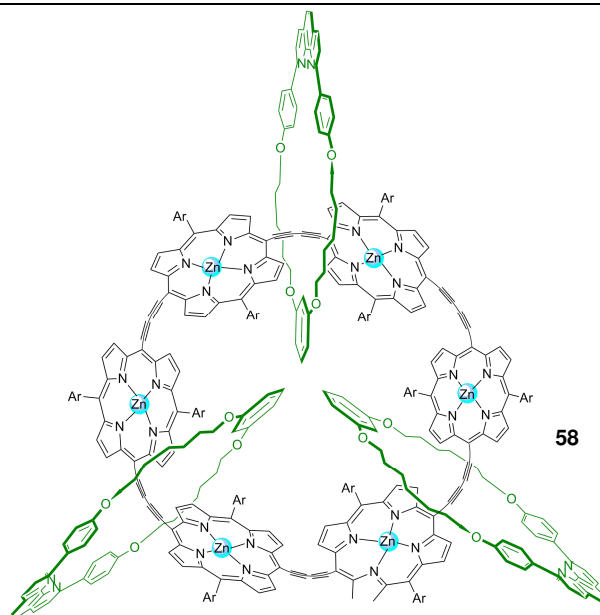
**Scheme 1.18.** The proposed mechanism of active template Pd<sup>II</sup>-mediated alkyne homocoupling of alkyne in the presence of pyridine-based macrocycle **15** to form [2]rotaxane.

An alkyne homocoupling reaction mediated by Ni(II) and Cu(I) through a bimetallic template could also be used to assemble rotaxanes.<sup>48</sup> Apart from alkyne coupling reactions, a Cu(I) catalyzed **Ullmann C-S Bond formation** reaction could also be utilized in the active metal template strategy to generate [2]rotaxane **57**.<sup>49</sup> (Scheme 1.19)



**Scheme 1.19.** Saito's active template Cu<sup>I</sup>-catalyzed Ullmann C-S bond forming reaction which generates [2]rotaxanes.

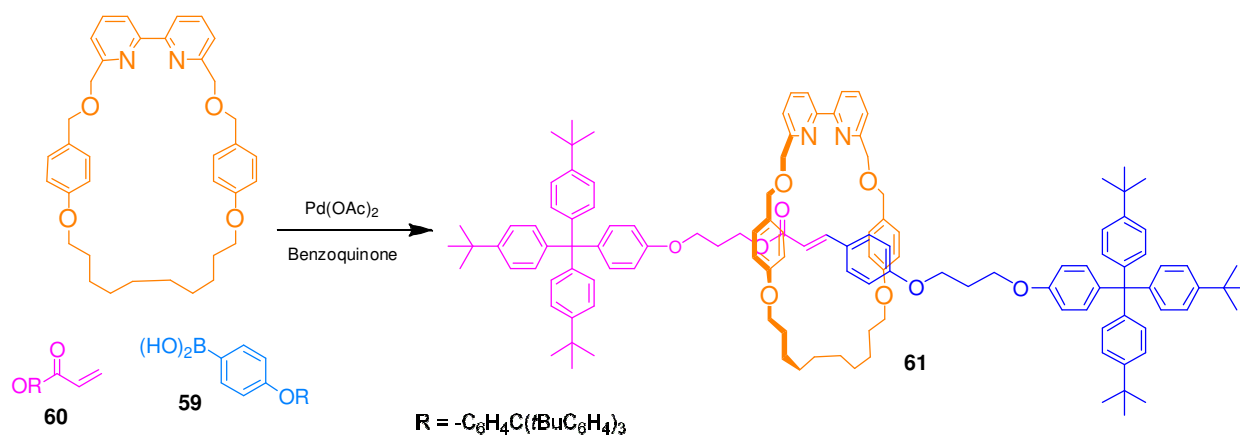
Recently, Anderson's group have synthesized [2]rotaxane which consist of butadiyne-linked porphyrin dimers threaded through a phenanthroline-containing macrocycle by an active-metal template directed copper-mediated Glaser coupling. The alkyne-terminated [2]rotaxane was transformed into a [4]catenane cyclic porphyrin hexamer **58** (Figure 1.13) by using a radial hexa-pyridyl template to aid the palladium-catalyzed Glaser coupling cyclisation.



**Figure 1.13.** Anderson's [4]catenane cyclic porphyrin hexamer by palladium catalyzed Glaser coupling via directed template strategy.

### 1.3.2.4 Pd(II) oxidative Heck Coupling AMT Reactions

A Pd(II) oxidative Heck coupling reaction was reported in 2007 as an addition to the AMT strategy.<sup>50</sup> (Scheme 1.20) Oxidation of the Pd(0) complex is required in this strategy due to the difficulty of coordinating Pd(0) to the macrocyclic ligand, the oxidative Heck reaction uses Pd(II) instead was successfully applied to obtain rotaxanes. Aryl boronic acid **59** (also electron rich and electron poor derivatives) and activated olefins such as vinyl esters **60**, vinyl ketones and styrenes were able to be applied in this method demonstrating the highly tolerant nature of this reaction.



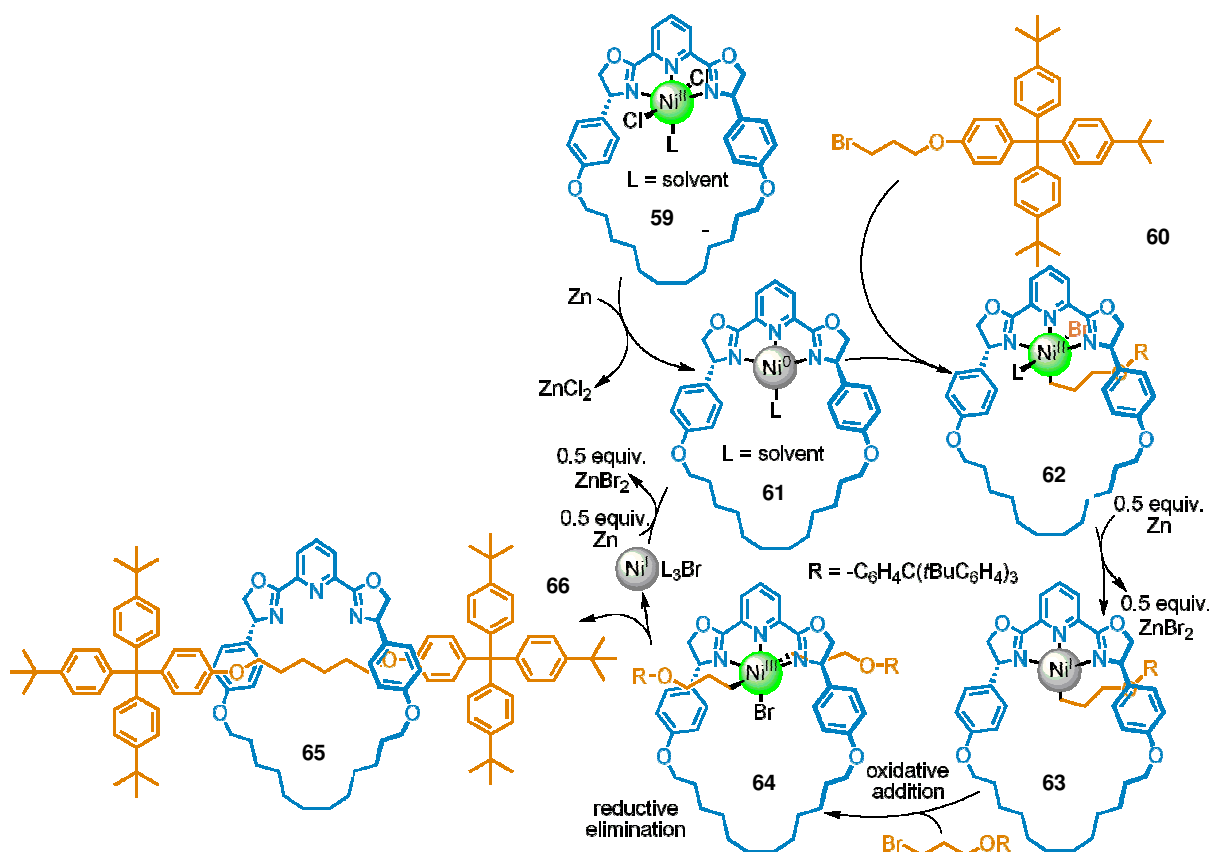
**Scheme 1.20.** Pd(II) oxidative Heck coupling reactions could be also successfully achieved [2]rotaxane **61**.

Metal ions have been used in AMT strategies in which they act as Lewis acid catalysts. For example in Michael additions or Diels-Alder cycloadditions which successfully formed rotaxanes in surprisingly high yields by Leigh et al.<sup>51</sup> In the latter example, the active template reaction selects 2-substituted cyclopentadienes over 1-substituted cyclopentadienes to react with the dienophile which generates the interlocked [2]rotaxanes.

#### 1.3.2.5 Alkyl-Alkyl Coupling AMT Reactions

Apart from alkyne-alkyne coupling reactions, more challenging reaction conditions could also be applied into the active metal template strategy. **Alkyl-Alkyl Coupling reactions**, for instance, have also been investigated in this template strategy by Leigh.<sup>52</sup> Scheme 1.21 shows that the active template rotaxane-forming reaction achieves an unusual transformation utilizing a pybox-based macrocyclic ligand. Furthermore, the mechanistic pathway experiments carried out are consistent with a Ni(II)-alkyl species **62** being reduced to the Ni(I)-intermediate **63** by Zn, which then oxidatively adds to another equivalent of the inactivated alkyl bromide. This oxidative addition was proven as the isolation of the interlocked product indicated that the reaction must proceed through the cavity of the macrocycle generating the threaded complex **64** which then reductively eliminates in a concerted fashion to give [2]rotaxane **65**. The Ni(I) complex **66** can then be reduced to Ni(0) by Zn thereby restarting the catalytic cycle.





**Scheme 1.21.**  $\text{Ni}^{\text{II}}$ -mediated active template  $\text{sp}^3$ - $\text{sp}^3$ -carbon coupling reaction for the synthesis of [2]rotaxanes

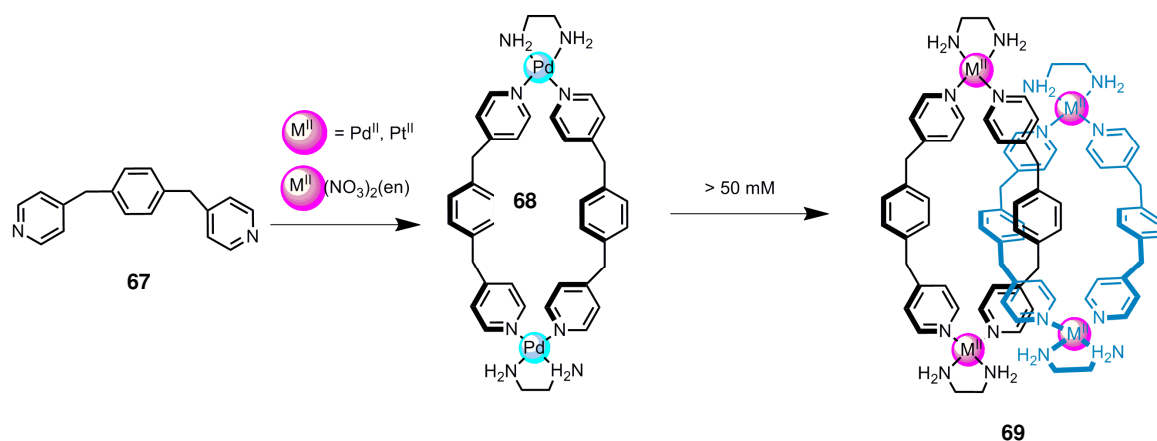
## 1.4 Hybrid Organic Inorganic interlocked structures

The rich variation in properties (preferred coordination number, ligand donor type and primary coordination geometry) of metals has led to an exotic selection of [2]catenanes containing metal ions as an integral part of their structure being reported in the literature. The relationship between these and the above complexes, other than their obvious topological congruity, is that their assembly is carried out under thermodynamic control. Evidently, a cyclic structure containing reversible coordinate bonds can reorganize to form a stable interpenetrated metal complex provided the energetic gain in stability achieved through inter-component recognition outweighs the entropic cost of unifying the two species.

### 1.4.1 Fujita's Achievement: A Catenane Incorporating Metal Ions Within its Framework

In 1994, this field of research was dominated by the work of Fujita, who reported a Pd(II) containing [2]catenane accessed via the quantitative self-assembly of simple component molecules.<sup>53</sup>

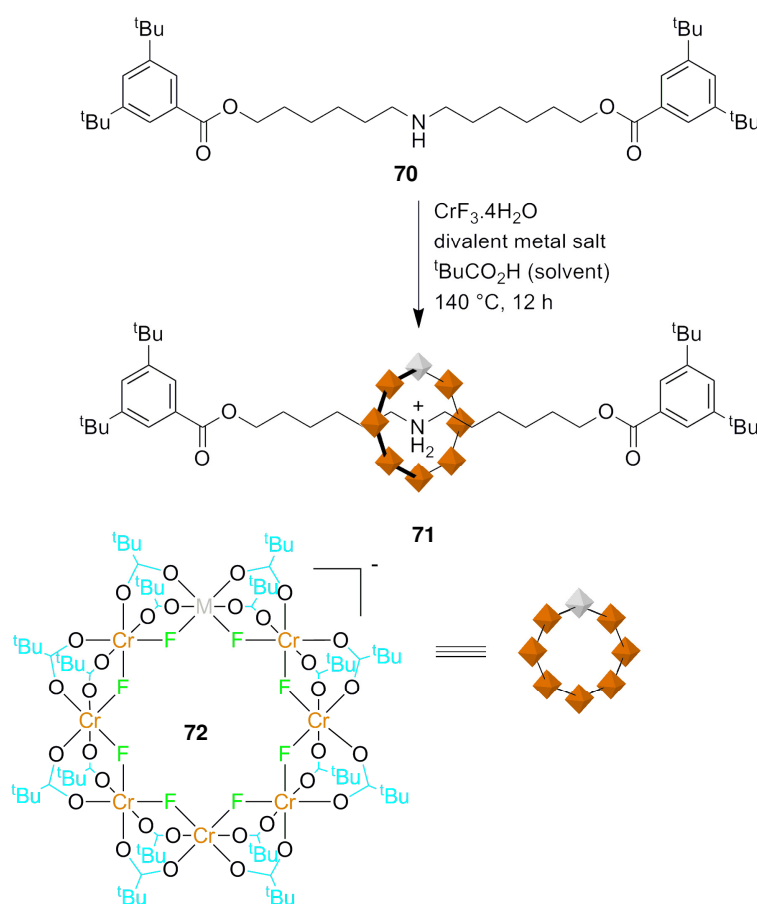
By mixing  $\text{Pd}(\text{NO}_3)_2(\text{en})$  with 1,4-bis[(4-pyridyl)methyl]benzene **67** in aqueous solution, macrocycle **68** and corresponding [2]catenane **69** were shown by  $^1\text{H}$  NMR to be in rapid equilibrium with one another (Scheme 1.22). Consequently, by Le Chatelier's Principle, at concentrations of greater than 50 mM, the reaction conditions favored the single component [2]catenane species **69**.<sup>54</sup> It has been suggested that the [2]catenane spontaneously forms as a result of double molecular recognition, i.e. the molecules bind each other in their respective hydrophobic cavities.<sup>55</sup> By increasing the polarity of the reaction medium through addition of  $\text{NaNO}_3$ , the yield of [2]catenane **69** was increased to greater than 99% even at high dilution, which supports this hypothesis.<sup>56</sup>



Scheme 1.22. Fujita's original Pd(II) catenane synthesis.

### 1.4.2 Hybrid Organic Inorganic Interlocked Structures

An assembly of a mixed metal ring in the formation of [2]rotaxane **71** afforded hybrid organic inorganic interlocked structures, as developed by the Leigh group.<sup>57</sup> Using an organic thread (such as **70**) to assemble a predominantly inorganic metallic ring is a new methodology. The rotaxane **71** and pseudorotaxane have been obtained in acceptable yield, containing threads that were utilized to neutralize the heterometallic ring **72**. (Scheme 1.23) Further details of the synthesis of a hybrid organic-inorganic catenane will be discussed in chapter 5.



**Scheme 1.23.** Hybrid organic inorganic interlocked molecules by assembly of the metal ring with a secondary amine thread.

## 1.5 State of the Nano-Art: Molecular Trefoil Knot and Borromean Rings

### 1.5.1 Molecular Trefoil Knot

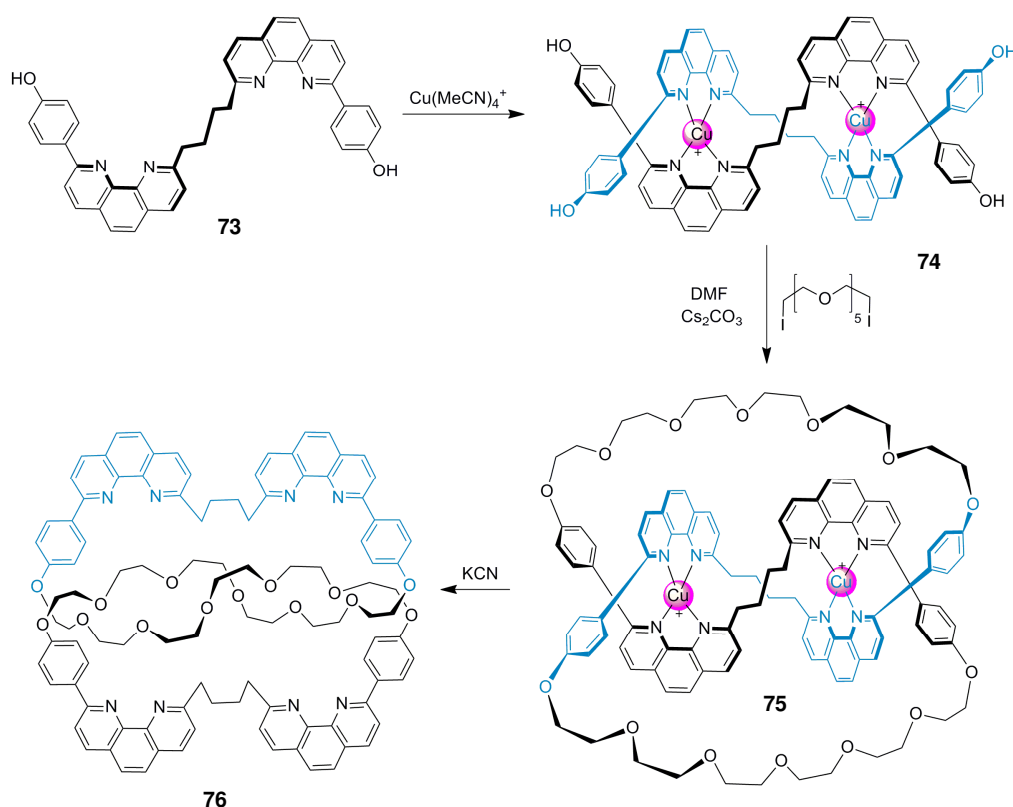
As the simplest example of a nontrivial knot, a trefoil knot, which cannot be untied without scission of its backbone, attracted most attention in early topological chemistry. The first successful synthesis strategy was realized through the extension of Sauvage's catenane formation. It was proposed that by the use of an extended-catenane ligand, it would be possible to access a double strand or helicate increasing the number of crossing-points forming the knot precursors (Scheme 1.24).<sup>58</sup>

Although many different approaches to catenanes and rotaxanes have been developed in recent years, few strategies have been successfully introduced for the synthesis of higher order molecular knots (apart from the topologically-trivial unknot (i.e. a simple macrocycle)). Trefoil knots have been found in types of DNA, proteins and in synthetic polymers<sup>59</sup>. Wasserman and Cozarelli defined the first naturally occurring catenated DNA as "Biochemical Topology".<sup>60</sup> This discovery and its extension to the development of knotted DNA have also influence significantly the field of designing and synthesizing mechanically interlocked compounds.

Schill and co-workers conceived and attempted direct synthesis methods towards a trefoil knot before the 1980s.<sup>61</sup> This strategy, which relied on a benzoacetal central core, is closely related to the one used to prepare catenanes. Unfortunately no desired product could be identified in this case.

In an extension from the Strasbourg strategy, originally designed for the synthesis of catenanes, Sauvage and co-worked used the linking of helicates with multiple turns to form the first molecular trefoil knot. Sauvage reported the first molecular trefoil knot in 1989<sup>62</sup> with its intertwined topology confirmed irrefutably by X-ray crystallography clearly showing the helical twist about the Cu(I) centers exploited to generate the required three crossing points. Ligand **73** used to fashion the first knot is shown in scheme 1.24. The short (CH<sub>2</sub>)<sub>4</sub> linker between the two phen units was used to reduce the complexation of the ligand around a single Cu(I) ion, but it was observed that the desired helical complex **74** was relatively labile and thus able to

interconvert with its co-planar analogue. After cyclisation to **75** and demetallation, a knotted system was obtained. This facile process led to a modest 3% yield of **75** following cyclisation. This was increased to 29% by replacing the  $(\text{CH}_2)_4$  linker with a 1,3-phenylene group (**73**→**75**).<sup>48</sup>



**Scheme 1.24.** Synthesis of a trefoil knot.

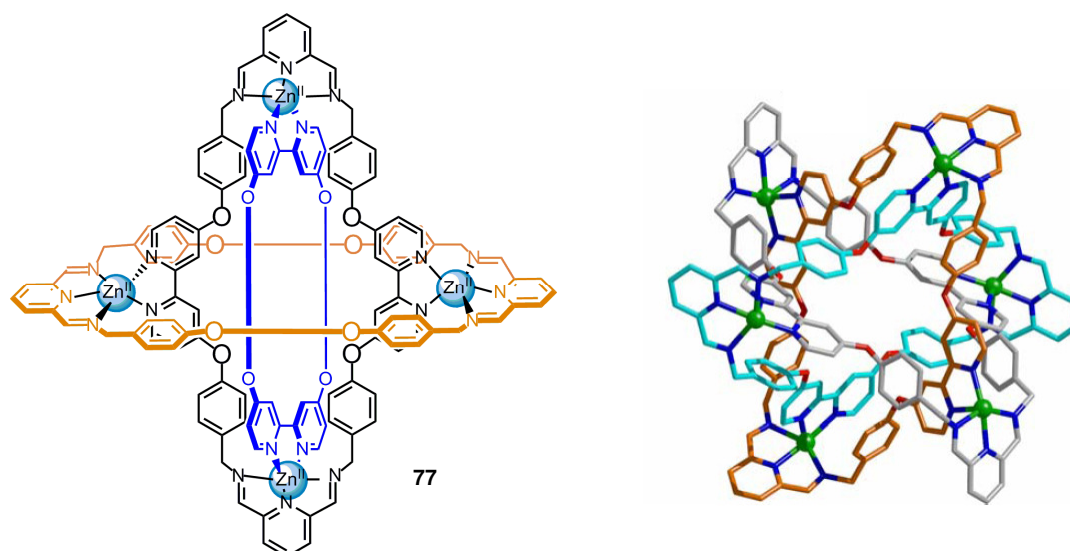
The trefoil knot synthesized by utilizing an octahedral metal ion has been subsequently further studied.<sup>63</sup> A double octahedral template in which the chelation of  $\text{Fe}(\text{II})$  with the presentation of a hexadentate ligand by the use of two folded terpyridine-derived ligands was performed by Sauvage's group to generate the desired trefoil knots in 20% yield. Hunter and co-workers reported using a single octahedral metal templation strategy via the ligation of  $\text{Zn}(\text{II})$  with three folded bipyridine as an octahedral ligand to generate the required cross-over points.<sup>64</sup> After linking the terminal olefins by RCM, the desired trefoil knot was generated by this elegant synthesis.

After research and efforts for more than half century, donor–acceptor interactions, Watson–Crick base pairing,<sup>65</sup> amide hydrogen bonding<sup>66</sup> and ligand folding about a metal ion<sup>67</sup> have all been used to template the formation of molecular trefoil knots. The field of Chemical Topology was defined as ‘two identical objects containing the same atoms and chemical bond connectivities, but that cannot be interconverted by any deformative action in three dimensional space’. Further details of the AMT synthesis of a trefoil knot will be discussed in Chapter 4.

### 1.5.2 Metal Template Synthesis of Molecular Borromean Rings

Borromean Rings is known as the design of three interlinked circles where one ring threaded through one of the other rings but not interlocked, and also threaded by the other ring. The three rings are inseparable but once any one ring is removed, the other two will then fall apart. Borromean rings have been synthesized in many different strategies due to this fascinating property<sup>68</sup>, also, they have been used as a symbol of strength in unit.

A metal template strategy to Borromean rings has been remarkably investigated by Stoddart and co-workers<sup>69,70</sup>. Terminal primary amines and six 2,6-diformylpyridine ligands constructed as six-bipy-baed ligands which were directly assembled by six penta-coordinate Zn(II) metal ions to orient and form a homocircuit Borromean ring **77**. X-ray crystallography also indicates that non-covalent interactions in-between the ring structure. Similar strategy to self-assemble other Borromean rings in which different substitutions on the pyridine<sup>71,72</sup> or other transition metals (Cu(II), Co(II), Mn(II) and Cd(II))<sup>73</sup> were utilized has also been successfully achieved.



**Scheme 1.25.** Stodart's Borromean rings.

## 1.6 Summary and Overview

From statistical methods to the use of template methods there has been tremendous progress in the field of the synthesis of interlocked molecules. However, there are still some structures created so far that have been made using the recognition set provided to us by nature in the form of DNA, which is the most inspiring supramolecular system in relation to its form, function and performance, that have still to be synthesized from small molecules.

There will be more developments and a progression to make larger, more complex structures and superstructures from small and simple building blocks. It is necessary for the design and synthesis of the components to be more precise and to achieve the progress of the “pre-programming” needed to be incorporated into the molecular components.

As a great deal of research into the methods of synthesizing interlocked molecules have been well developed and studied. How to prepare the more complicated molecular knots and higher order links is a new, fascinating and challenging subject for the scientist to discover the solutions.

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## Chapter 2

# **En Route to a Molecular Sheaf: Active Metal Template Synthesis of a [3]Rotaxane With Two Axles Threaded Through One Ring**

Published as '*En Route to a Molecular Sheaf: Active Metal Template Synthesis of a [3]Rotaxane With Two Axles Threaded Through One Ring.*' Hei Man Cheng, David A. Leigh, Francesca Maffei, Paul R. McGonigal, Alexandra M. Z. Slawin and Jhenyi Wu. *J Am Chem Soc*, **2011**, 133, 12298-12303.

## Synopsis

*We report that a 2,2':6',2''-terpyridylmacrocycle-Ni complex can efficiently mediate the threading of two alkyl chains with bulky end groups in an active metal template  $sp^3$ -carbon-to- $sp^3$ -carbon homocoupling reaction, resulting in a rare example of a doubly-threaded [3]rotaxane in up to 51% yield. The unusual architecture is confirmed by X-ray crystallography (the first time that a one-ring-two-thread [3]rotaxane has been characterized in the solid state) and is found to be stable with respect to dethreading despite the large ring size of the macrocycle. Through such active template reactions, in principle a macrocycle should be able to assemble as many axles in its cavity as the size of the ring and the stoppers will allow. A general method for threading multiple axles through a macrocycle adds significantly to the tools available for the synthesis of different types of rotaxane architectures.*

## Acknowledgements:

The following people are gratefully acknowledged for their contribution to this chapter: Hei Man Cheng and Dr. Francesca Maffei synthesized compounds **12** and **13**. Most of synthesis and investigation were performed by the author. Dr. Paul R. McGonigal had crucial input to the project and writing process. The crystals structure was solved by Prof. Alexandra Slawin.



## 2.1 Introduction

Rapid advances in many aspects of template synthesis, ligand design and methods for covalent capture are allowing access to increasingly complex mechanically interlocked architectures.<sup>1</sup> However, whilst there are numerous examples of rotaxanes consisting of several rings threaded onto a single axle,<sup>2,3</sup> rotaxanes featuring multiple axles passing through a single ring remain rare.<sup>4-6</sup> This disparity is accounted for by the relative structural demands on the cyclic component(s) and thread(s). The structural elements used for the synthesis of a [2]rotaxane can, in principle, be extrapolated to multi-ring rotaxanes with relative ease by simply employing an elongated axle with several template sites without changing the size and nature of the macrocycle or stoppers.<sup>2</sup> The synthesis of multi-thread rotaxanes is more challenging: The ring may require more than one template site to assemble multiple threads (using traditional template methods), and must be considerably larger than required for a [2]rotaxane in order to accommodate more than one axle, an issue that is further complicated by the sheer size of the stoppers required to prevent de-threading of large macrocycles.<sup>4b,c,e,7</sup> Furthermore, the macrocycle-thread interactions that direct the assembly of the interlocked components must overcome the sometimes severe steric clashes that can occur between crowded thread units.

Active metal template synthesis<sup>8</sup> is a strategy for the construction of mechanically interlocked architectures in which a macrocycle-bound transition metal ion acts as both the template to entwine or thread the components and as a catalyst to promote the covalent bond forming reaction that captures the interlocked structure. Unlike traditional 'passive' metal template approaches to the synthesis of rotaxanes,<sup>9</sup> a permanent metal binding site is only required on the macrocycle—the thread component may have little<sup>8a-e,g,k,m</sup> or no<sup>8n</sup> binding affinity for the transition metal ion after rotaxane formation. Thus the metal ion may be able to turn over during the reaction, a corollary being that in some cases only a sub-stoichiometric amount of the metal is required to achieve the transformation.<sup>8a,c-e,k</sup> Here we report on a further consequence of employing such a catalytic template system: a single active template site in a suitably large macrocycle is able to mediate the sequential

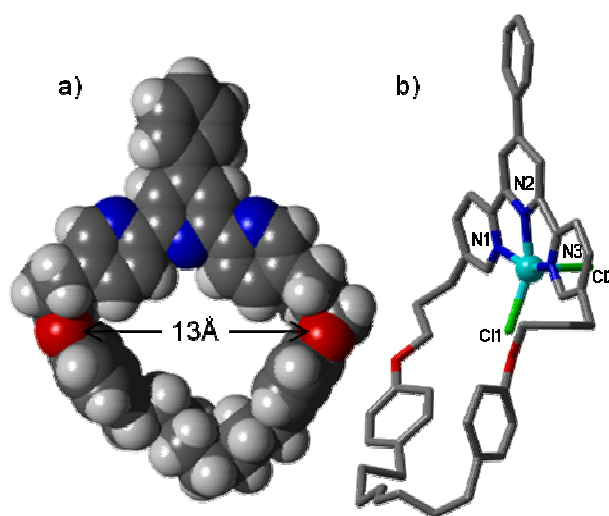
formation of two threads through one ring, giving rise to a doubly-threaded [3]rotaxane. To do so the cavity of the macrocycle must be large enough to accommodate two axes yet still small enough to prevent de-threading. A 35-membered ring with an endotopic 2,2':6',2''-terpyridine (terpy) binding site successfully promotes one-ring-two-threads [3]rotaxane formation via an active template Ni-catalyzed homocoupling of alkyl bromides terminated with tris(*t*-butylphenyl)methyl groups in up to 51% yield in a simple one-pot reaction.

## 2.2 Results and Discussion

We recently reported the discovery of a Ni-catalyzed  $sp^3$ -carbon-to- $sp^3$ -carbon alkyl bromide homocoupling reaction and its application to the active metal template synthesis of [2]rotaxanes.<sup>8n</sup> An essential feature of the reaction is the use of a tridentate nitrogen-donor-atom ligand to inhibit competing  $\beta$ -hydride elimination of alkyl-Ni intermediates during the Ni-catalyzed reductive dimerization. [2]Rotaxane formation was demonstrated using a macrocyclic pyridine-2,6-bisoxazoline ligand. However, the bisoxazoline macrocycle and rotaxane were prone to decomposition, limiting the scope of the reaction. Optimization of the Ni-catalyzed dimerization protocol with commercially available substrates revealed that terpy groups are also suitable catalyst ligands for this transformation and are much more stable than oxazoline units.<sup>8n,10</sup> It appeared that integration of the robust terpy binding motif into a macrocycle might overcome the rotaxane stability issue, enabling the Ni-catalyzed alkyl bromide homocoupling reaction to be rather more synthetically useful.

Macrocycle **1** was synthesized from commercially available 2,5-dibromopyridine and 4-(4-methoxyphenyl)-butyl bromide in 24% overall yield, with 8 steps in the longest linear sequence (for details of the synthesis see 2.4 Experimental Section). Substitution at the 5- and 5''- position of the terpy ring system allows rotation of the pyridyl rings relative to one another<sup>11</sup> upon chelation of Ni<sup>II</sup> and the 120° turn angle of the rigid aromatic framework induces cavity dimensions appropriate for use in rotaxane-forming reactions. Single crystals of both macrocycle **1** and the

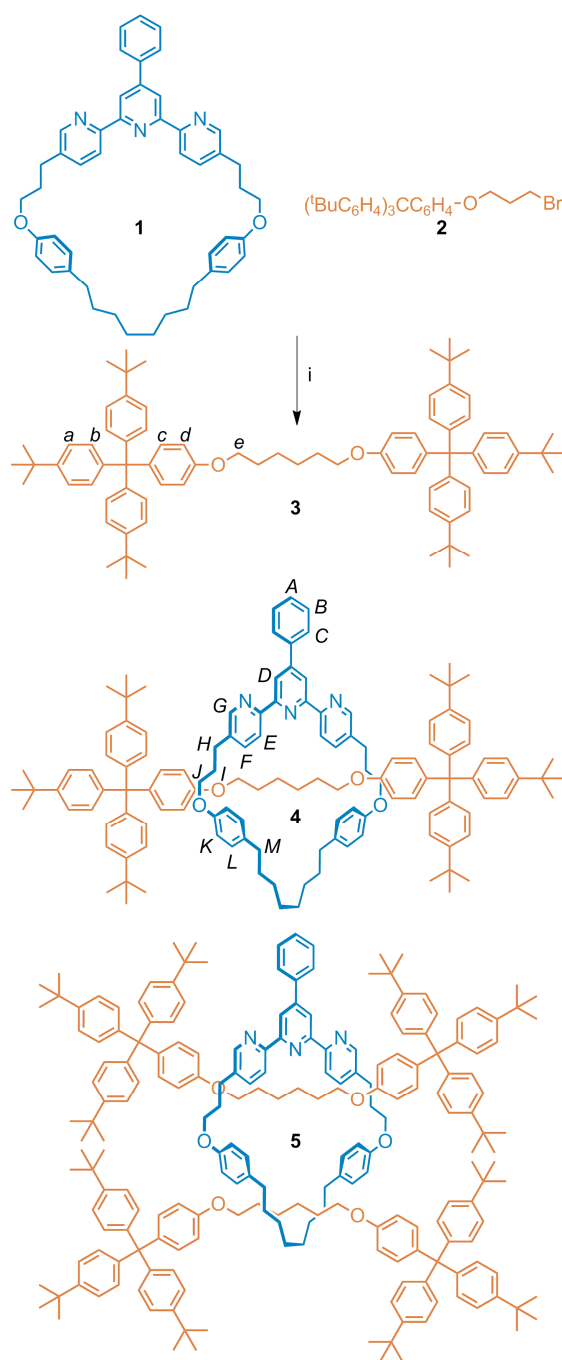
corresponding complex **1**.NiCl<sub>2</sub> were obtained by slow vapor diffusion of diethyl ether or methanol into chloroform solutions and the solid state structures determined by X-ray crystallography (Figure 2.1). The crystal structure of **1** shows that the rigid terpy portion of the macrocycle generates an aperture with a cavity width of up to 13 Å (Figure 2.1a). The terpyridyl ring system switches to a *cis-cis* geometry upon coordination to Ni<sup>II</sup> (Figure 2.1b), holding the metal center endotopically as required for a rotaxane-forming active template mechanism.



**Figure 2.1.** X-Ray crystal structure of a) macrocycle **1**, from a single crystal obtained by vapor diffusion of diethyl ether into a chloroform solution, space filling representation, and b) complex **1**.NiCl<sub>2</sub>, from a single crystal obtained by slow diffusion of methanol into a chloroform solution, stick representation. Solvent molecules and hydrogen atoms of **1**.NiCl<sub>2</sub> are omitted for clarity. Nitrogen atoms are shown in blue, oxygen atoms red, chlorine atoms green, nickel atoms cyan (ball), hydrogen atoms white and carbon atoms gray. Selected bond lengths [Å] and angles [°]: N1-Ni 2.11, N2-Ni 1.97, N3-Ni 2.12, Cl1-Ni 2.27, Cl2-Ni 2.30, N1-Ni-N2 77.1, N1-Ni-N3 153.5, N2-Ni-Cl1 154.0, Cl1-Ni-Cl2 108.0, N2-Ni-Cl2 98.0.

The catalytically-active macrocycle–Ni<sup>0</sup> complex was formed *in situ* by stirring **1** with NiCl<sub>2</sub>•6H<sub>2</sub>O in *N*-methyl-2-pyrrolidone (NMP) followed by reduction with Zn powder. After addition of a solution of the ‘stoppered’ alkyl bromide **2** in tetrahydrofuran (THF), the reaction mixture was heated at 60 °C for 18 h (Scheme 2.1 and Table 2.1) then demetallated with a basic ethylenediaminetetraacetic acid disodium salt-ammonia (Na<sub>2</sub>EDTA-NH<sub>3</sub>) solution.<sup>12</sup> Pleasingly, a stoichiometric amount of stoppered bromide **2** led to complete conversion to homocoupled products and

formation of the desired [2]rotaxane **4** as observed by analysis of the crude reaction mixture by  $^1\text{H}$  NMR spectroscopy and mass spectrometry. Purification of the crude reaction mixture by size-exclusion chromatography revealed only a modest 14% yield of [2]rotaxane **4** (Table 2.1, entry 1). However, as the catalytic Ni complex can turn over during the reaction, the yield of [2]rotaxane could be increased to 48% by employing a 2.5-fold excess of bromide **2** (Table 1, entry 2). To our surprise, when a 5-fold excess of bromide **2** was used in an attempt to further increase the amount of **4** formed, the isolated yield of [2]rotaxane fell to 29% (Table 2.1, entry 3). The reason behind this unexpected drop in yield of **4** became apparent during the size-exclusion purification procedure: a substantial amount of material eluted before the [2]rotaxane indicating another product with a larger hydrodynamic volume.  $^1\text{H}$  NMR Spectroscopy and mass spectrometry revealed that the second product was the one-ring-two-thread [3]rotaxane **5** (Scheme 2.1).<sup>13</sup> Repetition of the reaction protocol using less equivalents of **2** (Table 2.1, entries 1 and 2) confirmed small amounts (<10%) of **5** are also formed under those conditions. The [3]rotaxane proved to be the major product when using a 10-fold excess of bromide **2**, producing a total of 71% interlocked products of which 51% was [3]rotaxane **5** (Table 2.1, entry 4). As complete conversion of **2** occurred and unconsumed macrocycle **1** could be recovered, the yield of interlocked products reflects the proportion of intermediate dialkyl-Ni species that react with the axle precursors protruding from opposite faces of the macrocycle (leading to rotaxane **4** or **5**) or from the same face (leading to the non-interlocked axle **3**). Unlike the bisoxazoline-macrocycle rotaxanes previously prepared using the Ni-catalyzed active metal template  $\text{sp}^3$ -carbon-to- $\text{sp}^3$ -carbon homocoupling reaction,<sup>8n</sup> the terpy-macrocycle-based [2]rotaxane **4** and [3]rotaxane **5** proved completely stable (no degradation observed over several months, *vide infra*).



**Scheme 2.1.** Synthesis of [2]- and [3]Rotaxanes via a Nickel-Catalyzed Active Template Reductive Homocoupling Reaction.<sup>a</sup>

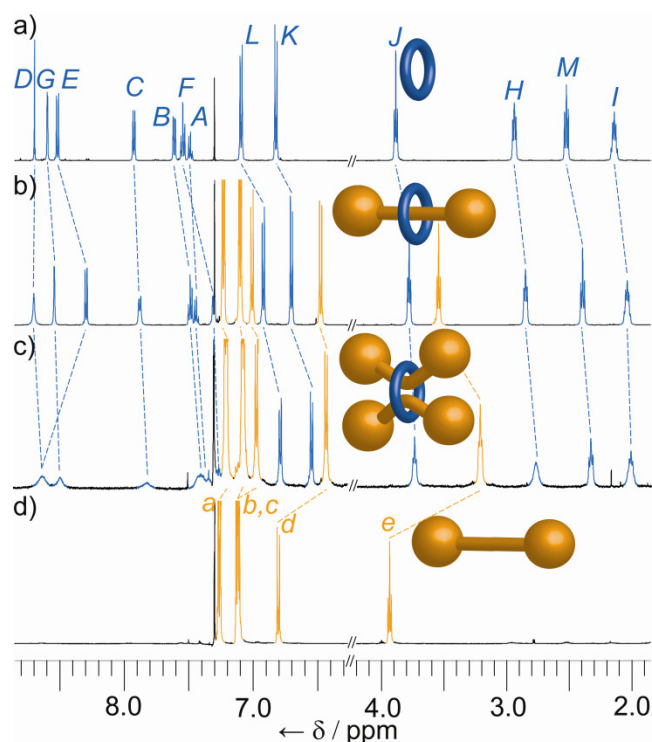
<sup>a</sup> Reagents and conditions: (i) 1.  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ , Zn, NMP-THF (1:1), 60 °C, 18 h. 2.  $\text{Na}_2\text{EDTA-NH}_{3(\text{aq})}$ .

**Table 2.1.** Conversion of Macrocycle **1** to [2]Rotaxane **4** and [3]Rotaxane **5** (Scheme 1).

Entry	Equiv. <b>2</b>	[2]Rotaxane <b>4</b> yield <sup>a</sup>	[3]Rotaxane <b>5</b> yield <sup>a</sup>
<b>1</b> <sup>b</sup>	2.0	14%	4%
<b>2</b> <sup>b</sup>	5.0	48%	9%
<b>3</b> <sup>b</sup>	10.0	29%	30%
<b>4</b> <sup>c</sup>	20.0	20%	51%

<sup>a</sup> Isolated yields based on macrocycle **1**. <sup>b</sup> 10 equiv. Zn. <sup>c</sup> 15 equiv. Zn. In all cases  $\geq 95\%$  conversion to homocoupled products was determined by <sup>1</sup>H NMR analysis of the crude reaction mixture.<sup>12</sup>

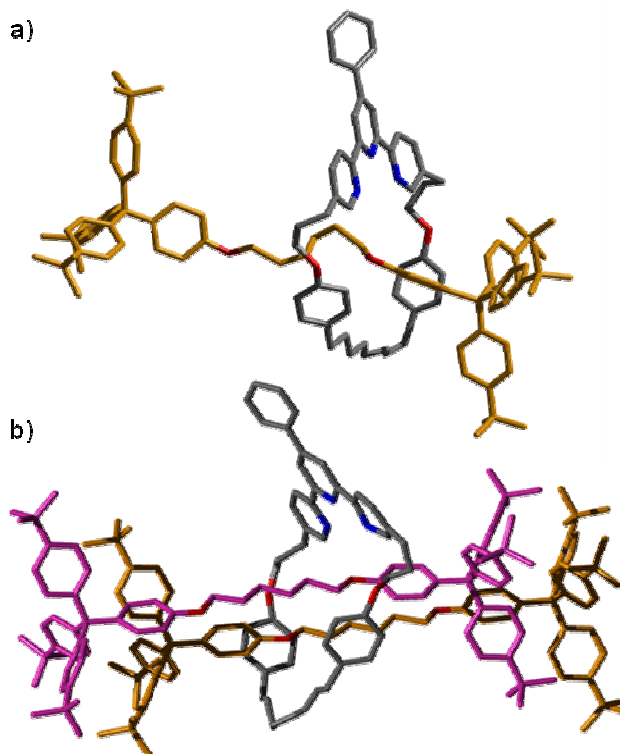
Comparison of the <sup>1</sup>H NMR spectrum (500 MHz, CDCl<sub>3</sub>, 298 K) of the [2]rotaxane **4** (Figure 2.2b) with those of its non-interlocked components (macrocycle **1** and thread **3**; Figures 2.2a and 2d respectively) shows upfield shifts of protons from the thread and macrocycle typical of regions of mechanically interlocked structures that spend some time face-on to aromatic rings. The uniform distribution of the modest shielding effects suggest that no particular co-conformation is stabilized—the macrocycle and thread can undergo relatively unrestricted motion relative to one another, as would be expected in a system with no strong intercomponent interactions. However, threading of a second alkyl chain axle through the ring ([3]rotaxane **5**, Figure 2.2c) results in increased shielding of most of the thread protons as they are forced to spend more time closer to the aromatic rings of the macrocycle. Several of the macrocycle resonances (H<sub>A-H</sub>) are broadened, possibly as a consequence of the steric congestion between the chains causing some co-conformational exchange processes, such as macrocycle pirouetting, to slow to rates close to the <sup>1</sup>H NMR timescale.



**Figure 2.2.** Partial  $^1\text{H}$  NMR spectra (500 MHz,  $\text{CDCl}_3$ , 298 K) of a) macrocycle **1**, b) [2]rotaxane **4**, c) [3]rotaxane **5**, and d) non-interlocked thread **3**. The lettering corresponds to that shown in Scheme 1.

Single crystals of **4** and **5** suitable for X-ray diffraction were grown by slow diffusion of methanol into solutions of each rotaxane in deuterated chloroform. The crystal structures (Figure 2.3) confirm the constitution of both rotaxanes and the doubly-threaded nature of [3]rotaxane **5**—the first time a one-ring-two-thread [3]rotaxane structure has been determined in the solid state. In the solid state the alkyl chain of the thread of [2]rotaxane **4** (Figure 3a) adopts a folded conformation where it passes through the ring ( $\text{C-C-C-C}$  dihedral angles  $50^\circ \leq \phi \leq 160^\circ$ ), apparently to occupy as much of the space within the macrocyclic cavity as possible, driven by crystal packing forces. In contrast, both alkyl chains of [3]rotaxane **5** adopt fully extended zigzag conformations ( $\text{C-C-C-C}$  dihedral angles  $\phi \approx 180^\circ$ )—there is comparatively little unfilled space remaining in the cavity of the doubly-threaded macrocycle—and are offset from one another by approximately  $4.5 \text{ \AA}$  along the vector of the thread which minimizes steric clashes between the bulky trityl stoppers. Avoiding stopper–stopper repulsion, perhaps through the use of longer threads, may be an important factor for extrapolating this methodology to the preparation of rotaxanes in which more than

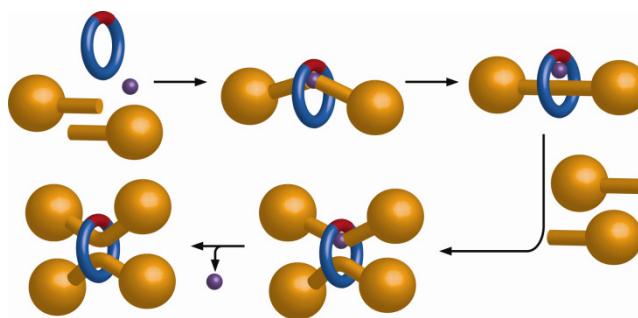
two axles are threaded through a single ring, particularly as the stopper size required to prevent dethreading increases dramatically with only small increases in macrocycle size.<sup>4b,c,e,7</sup>



**Figure 2.3.** X-Ray crystal structures of a) [2]rotaxane **4**, and b) [3]rotaxane **5**, from single crystal obtained by slow diffusion of methanol into deuteriochloroform solutions. Hydrogen atoms and solvent molecules are omitted for clarity. Nitrogen atoms are shown in blue, oxygen atoms red and the carbon atoms of the different components in gray, gold and pink.

The formation of [3]rotaxane **5** likely proceeds in a step-wise manner via a [2]rotaxane intermediate as depicted schematically in Figure 4. After active template assembly of the first axle (to give [2]rotaxane **4**), the catalytically active metal center is regenerated and can then gather another pair of building blocks and mediate the formation of a second covalent bond, furnishing the [3]rotaxane. Other active template reactions may also have the potential to form multiply threaded rotaxanes. However, the macrocycles used in previous studies have not possessed a cavity of a size capable of accommodating more than one thread and a metal ion simultaneously.<sup>8</sup>





**Figure 2.4.** Active metal template synthesis of [3]rotaxanes. A macrocyclic ligand (blue) with an endotopic binding site (red) coordinates to a metal ion (purple). The metal can mediate the construction of interlocked products by promoting the formation of covalent bonds through the cavity. If the ring is large enough to accommodate two threads and the catalytic metal center can turn over, a doubly-threaded [3]rotaxane can be assembled in a simple one-pot procedure.

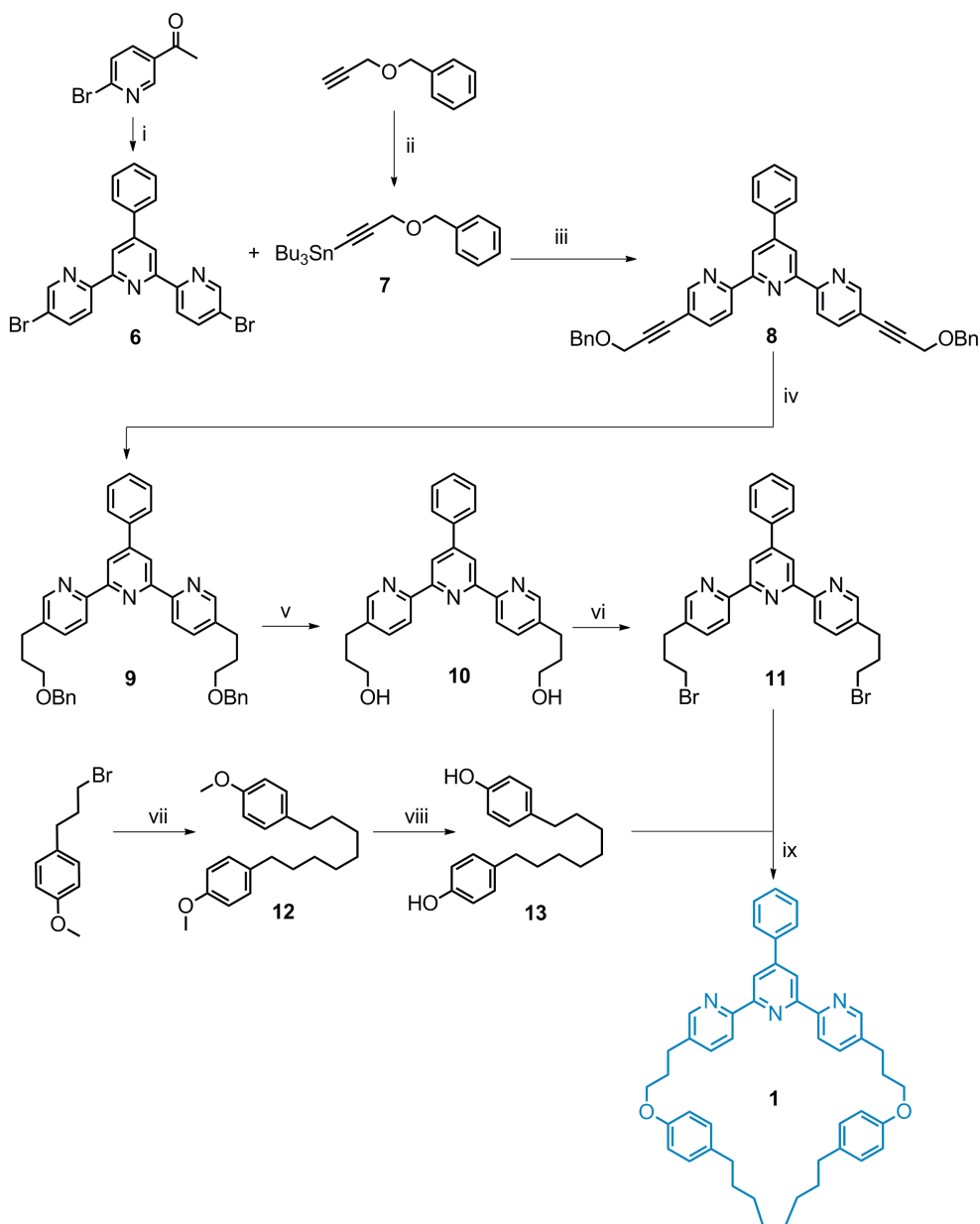
The paucity of doubly-threaded rotaxanes in the literature<sup>4</sup> stems from the delicate balance that must be struck between the relative dimensions of the components in order to successfully entrap two axles in one ring—the macrocycle must possess a cavity large enough to accommodate both threads but should not be so large as to be able to slip over the stoppering groups. Indeed, in previously reported syntheses of doubly-threaded [3]rotaxanes around an octahedral metal template<sup>4c</sup> or using DNA building blocks<sup>4e</sup> removal of the template interaction results in metastable structures that dethread over several hours or days at ambient temperature, illustrating the general trade-off between synthetic accessibility and stability for such structures. Neither [2]rotaxane **4** nor [3]rotaxane **5** showed any signs of dethreading over several months at ambient temperature or upon heating for several hours at 60 °C (see 2.4 Experimental Section). As [2]rotaxane **4** is stable, isolable and can be obtained in good yield (up to 48%; Table 2.1, entry 2), it may be useful as an intermediate for the synthesis of [3]rotaxanes with two constitutionally different threads,<sup>4a,e</sup> ring-in-ring complexes<sup>14</sup> and for the stepwise assembly of more complex interlocked architectures, such as heterocircuit Borromean rings.

## 2.3 Conclusions

2,2':6',2''-Terpyridyl macrocycle **1** is a highly effective ligand for the Ni-catalyzed active template  $\text{sp}^3$ -carbon-to- $\text{sp}^3$ -carbon homocoupling of alkyl bromides to form chemically robust and kinetically stable rotaxanes. The axles of the rotaxanes are simple alkyl chains (terminated with suitably bulky groups to prevent dethreading) rendering the synthesis effectively traceless in terms of the structure of the threads. The cavity of the 35-membered ring of **1** is sufficiently small that tris(*t*-butylphenyl)methyl groups can act as the stoppers, but large enough that two alkyl chain threads can be accommodated within the cavity. A one-ring-two-thread [3]rotaxane **5** was isolated in up to 51% yield in a simple one-pot procedure from a five component reaction that features two mechanical bond-forming steps. A small increase in macrocycle size may enable higher order multiply-threaded rotaxanes to be synthesized, e.g. a ring clasping three threads in its cavity, a type of molecular architecture for which no examples exist to date. Ways of using this, presently unique, synthetic tool for assembling sheaves<sup>15</sup> of molecular chains with no recognition elements<sup>6</sup> are currently being investigated in our laboratory.

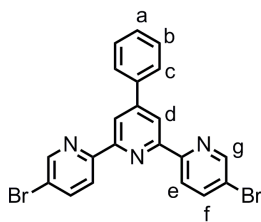
## 2.4 Experimental Section

### 2.4.1 Experimental Procedures



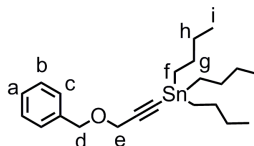
**Scheme 2.2.** Synthesis of macrocycle **1**.<sup>a</sup>

<sup>a</sup> Reagents and conditions: i) KOH, EtOH, PhCHO,  $\text{NH}_3(\text{aq})$ , rt, 18 h, 65%. ii) 1.  $n\text{-BuLi}$ ,  $n\text{-hexane}$ , THF, 0 °C, 1 h; 2.  $(n\text{-Bu})_3\text{SnCl}$ , rt, 18 h, 72%. iii)  $\text{Pd}(\text{PPh}_3)_4$ , DMF, 110 °C, 18 h, 92%. iv)  $\text{H}_2$ ,  $\text{PtO}_2$ , EtOH, THF, rt, 18 h, 97%. v)  $\text{Me}_3\text{SiH}$ ,  $\text{CH}_2\text{Cl}_2$ , 50 °C, 18 h, 63%. vi) 1.  $\text{Et}_3\text{N}$ ,  $\text{MsCl}$ ,  $\text{CH}_2\text{Cl}_2$ , -5 °C  $\rightarrow$  rt, 2 h; 2.  $\text{LiBr}$ , acetone,  $\Delta$ , 4 h, 85%. vii)  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ , 2,2':6',2''-terpyridine, Zn, DMF, rt, 18 h, >99%. viii)  $\text{Me}_3\text{SiH}$ ,  $\text{CHCl}_3$ , 50 °C, 48 h, >99%. ix)  $\text{Cs}_2\text{CO}_3$ , DMF, 60 °C, 48 h, 60%.



## 6

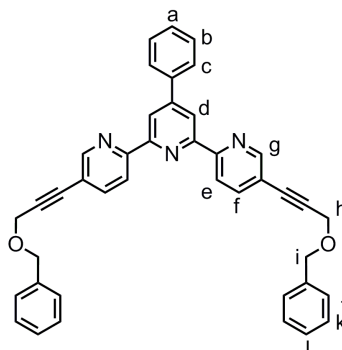
2-Acetyl-5-bromopyridine<sup>16</sup> (1.68 g, 9 mmol) was added to a solution of benzaldehyde (0.73 g, 4.5 mmol) in EtOH (35 ml). KOH pellets (1.10 g, 85%, 9 mmol) and an aqueous solution of NH<sub>3</sub> (17 ml, 35% w/w) were then added and the resulting solution stirred at rt for 18 h. After this time a precipitate formed which was isolated by filtration and washed with EtOH. Recrystallisation of this crude product from CHCl<sub>3</sub> afforded (1.37 g, 65%) **6** as a colorless crystalline solid. M.p. 232–234 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 8.77 (d, 2H, *J* = 2.4, H<sub>g</sub>), 8.72 (s, 2H, H<sub>d</sub>), 8.54 (d, 2H, *J* = 8.8, H<sub>e</sub>), 7.99 (dd, 2H, *J* = 8.8, 2.0, H<sub>c</sub>), 7.89 – 7.86 (m, 2H, H<sub>b</sub>), 7.55 – 7.45 (m, 3H, H<sub>a+f</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 155.9, 154.1, 150.1, 149.8, 139.5, 129.1, 128.8, 126.9, 122.6, 121.1, 127.2, 118.8; LRAPCI-MS: *m/z* = 466 [M+H]<sup>+</sup>; HRESI-MS: *m/z* = 465.9532 (calcd. for C<sub>21</sub>H<sub>14</sub>N<sub>3</sub>Br<sub>2</sub>, 465.9549) .



## 7

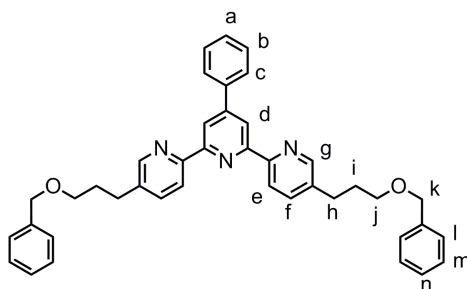
To a solution of benzyl propargyl ether (2.0 g, 14 mmol) in THF (20 mL) was added *n*-BuLi as a 1.6 M solution in *n*-hexane (8.6 mL, 14 mmol) dropwise at 0 °C. The solution was stirred for 1 h at 0 °C then tributyltin(IV) chloride (3.70 mL, 14 mmol) was added. The reaction mixture was then allowed to slowly warm to rt and stirred for 18 h. After removal of the solvent under reduced pressure, the residue was partitioned between Et<sub>2</sub>O (50 mL) and H<sub>2</sub>O (50 mL). The organic phase was dried (MgSO<sub>4</sub>) and concentrated under reduced pressure before purification of the resulting residue by column chromatography (petroleum ether with 3% EtOAc) gave **52** (4.4 g, 72%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.38 – 7.29 (m, 5H, H<sub>a+b+c</sub>), 4.63 (s, 2H, H<sub>e</sub>), 4.19 (s, 2H, H<sub>d</sub>),

1.62 – 1.53 (m, 6H, H<sub>f</sub>), 1.39 – 1.28 (m, 6H, H<sub>g</sub>); 1.04 – 0.98 (m, 6H, H<sub>f</sub>) ; 0.91 (t, 9H, *J* = 7.2, H<sub>i</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 137.7, 128.4, 128.2, 127.8, 105.8, 90.0, 71.1, 58.1, 28.9, 27.1, 13.7, 11.1.

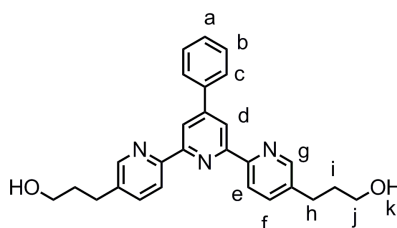


### 8

To a stirred suspension of **6** (0.82 g, 1.8 mmol) and **7** (3.00 g, 6.9 mmol) in anhydrous, degassed DMF (200 mL) was added tetrakis(triphenylphosphine) palladium(0) (0.30 g, 0.25 mmol) and the resulting reaction mixture was heated to 110 °C for 18 h. After evaporation of DMF *in vacuo*, the residue was diluted with a 1 M solution of KOH in MeOH (150 mL) and stirred for 1 h. The mixture was then further diluted with brine (100 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 100 mL). The combined organic extracts were extracted with H<sub>2</sub>O (100 mL), dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. Hexane (200 mL) was then added to the crude residue and the resulting precipitate was collected by filtration, washing on the filter with hexane (100 mL) to give **8** (990 mg, 92%) as a brown solid. M.p. 113–115 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 8.79 – 8.78 (m, 2H, H<sub>g</sub>), 8.75 (s, 2H, H<sub>d</sub>), 8.54 (dd, 2H, *J* = 8.8, 2.0, H<sub>e</sub>), 7.93 – 7.89 (m, 4H, H<sub>b+c</sub>), 7.89 – 7.86 (m, 13H, H<sub>a+f+j+k+l</sub>), 4.72 (s, 4H, H<sub>h</sub>), 4.77 (s, 4H, H<sub>i</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 155.3, 155.1, 151.8, 150.4, 139.6, 138.2, 137.2, 129.2, 129.0, 128.5, 128.2, 128.0, 127.3, 120.5, 119.7, 119.4, 89.4, 83.4, 72.0, 57.9; LRAPCI-MS: *m/z* = 598 [M+H]<sup>+</sup>; HRESI-MS: *m/z* = 598.2485 (calcd. for C<sub>41</sub>H<sub>32</sub>O<sub>2</sub>N<sub>3</sub>, 598.2489).

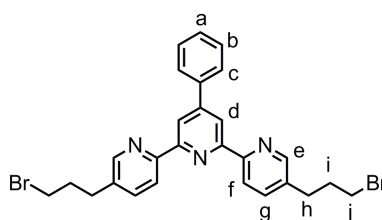
**9**

**8** (217 mg, 0.36 mmol) was dissolved in EtOH (24 mL) and THF (5 mL) then N<sub>2</sub> was bubbled through for 5 minutes before adding PtO<sub>2</sub> (17 mg g, 36 μmol). H<sub>2</sub> was bubbled through for 5 min and then the reaction mixture was allowed to stir under an atmosphere of H<sub>2</sub> at rt for 18 h. After filtration through a pad of celite, the solvent was evaporated under reduced pressure to give **9** (212 mg, 97%) as a yellow oil which was sufficiently pure to be taken on to the next step without further purification. M.p. 113–115 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 8.59 (s, 2H, H<sub>d</sub>), 8.51 – 8.44 (m, 4H, H<sub>e+g</sub>), 7.81 (d, *J* = 7.2, 2H, H<sub>c</sub>), 7.58 (dd, *J* = 8.2, 2.0, 2H, H<sub>b</sub>), 7.44 – 7.32 (m, 3H, H<sub>a+f</sub>), 7.30 – 7.16 (m, 10H, H<sub>l+m+n</sub>), 4.43 (s, 4H, H<sub>j</sub>), 3.43 (t, *J* = 6.2, 4H, H<sub>k</sub>), 2.72 (t, *J* = 7.6, 4H, H<sub>h</sub>), 1.95 – 1.81 (m, 4H, H<sub>i</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 156.0, 154.3, 150.3, 149.4, 138.7, 138.5, 137.6, 137.0, 129.0, 129.0, 128.5, 127.8, 127.7, 127.4, 121.1, 118.5, 73.1, 69.1, 31.1, 29.5; LRAPCI-MS: *m/z* = 606 [M+H]<sup>+</sup>; HRESI-MS: *m/z* = 606.3113 (calcd. for C<sub>41</sub>H<sub>32</sub>O<sub>2</sub>N<sub>3</sub>, 606.3115).

**10**

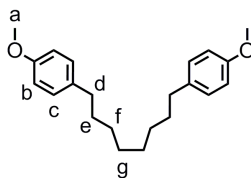
To a suspension of **9** (212 mg, 0.35 mmol) in CHCl<sub>3</sub> (3 mL) was added trimethylsilyliodide (1 mL, 0.7 mmol) and the resulting solution was stirred at 50 °C for 18 h. The reaction mixture was allowed to cool to rt and diluted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL) and extracted with a 17.5% aqueous solution of NH<sub>3</sub> saturated with Na<sub>2</sub>EDTA

(2×100 mL), H<sub>2</sub>O (3×100 mL) and brine (100 mL). The organic layer was dried (MgSO<sub>4</sub>), concentrated under reduced pressure and the resulting residue purified by column chromatography (neutral alumina, CH<sub>2</sub>Cl<sub>2</sub> with 5% MeOH) to give **10** (94 mg, 63%) as yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 8.65 (s, 2H, H<sub>d</sub>), 8.54 – 8.53 (m, 4H, H<sub>e+g</sub>), 7.88 (dd, 2H, *J* = 8.8, 2.0, H<sub>c</sub>), 7.66 (dd, 2H, *J* = 8.8, 2.0, H<sub>b</sub>), 7.51 – 7.43 (m, 3H, H<sub>a+f</sub>), 3.69 (t, 4H, *J* = 6.4, H<sub>j</sub>), 2.77 (t, 4H, *J* = 6.4, H<sub>h</sub>), 2.23 – 2.22 (br, 2H, H<sub>k</sub>), 1.95 – 1.88 (m, 4H, H<sub>i</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 155.8, 154.1, 150.1, 149.1, 138.4, 137.5, 136.8, 128.9, 127.2, 127.1, 121.1, 118.4, 61.6, 33.7, 29.0; LRAPCI-MS *m/z* = 426 [M+H]<sup>+</sup>; HRESI-MS: *m/z* = 426.2173 (calcd. for C<sub>27</sub>H<sub>28</sub>O<sub>2</sub>N<sub>3</sub>, 426.2176).

**11**

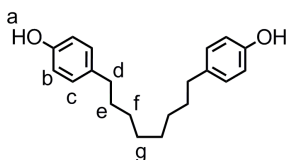
To a solution of **10** (94 mg, 0.22 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (14 mL) cooled to -5 °C was added Et<sub>3</sub>N (0.35 mL, 2.5 mmol) then methanesulfonyl chloride (0.1 mL, 1.1 mmol) and the resulting mixture stirred at 0 °C for 2 h. The reaction mixture was diluted with H<sub>2</sub>O (30 mL) and the phases separated. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (15 mL) and the combined organic extracts were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. The residue was dissolved in acetone (9 mL), LiBr (0.5 g, 5.8 mmol) was added and the reaction mixture was heated to reflux for 4 h. The reaction mixture was allowed to cool to rt then partitioned between CH<sub>2</sub>Cl<sub>2</sub> (100 mL) and H<sub>2</sub>O (100 mL). The phases were separated and the organic phase was extracted with H<sub>2</sub>O (3×100 mL) and brine (100 mL) then dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to give **11** (102 mg, 85%) as a brown oil. The crude product was sufficiently pure to be used without further purification and, as it was also prone to decomposition, was used in the following step immediately. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 8.67 (s, 2H, H<sub>d</sub>), 8.56 – 8.55 (m, 4H, H<sub>e+g</sub>), 7.87 (dd, 2H, *J* = 8.8, 2.0, H<sub>c</sub>), 7.67 (dd, 2H, *J* = 8.8, 2.0, H<sub>b</sub>), 7.50 – 7.40 (m, 3H, H<sub>a+f</sub>), 3.39 (t, 4H, *J* = 6.4, H<sub>j</sub>), 2.83 (t, 4H, *J* = 7.6, H<sub>h</sub>), 2.21 – 2.16 (m, 4H, H<sub>i</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 155.7, 154.3,

150.2, 149.2, 138.4, 136.9, 132.0, 128.5, 128.4, 127.2, 121.1, 118.5, 33.5, 32.5, 30.9; LRFAB-MS 3-NOBA matrix):  $m/z$  = 552  $[M+H]^+$ .



**12**

To a solution of 2,2':6',2''-terpyridine (44 mg, 0.19 mmol) and  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  (45 mg, 0.19 mmol) in DMF (7.6 mL) under an atmosphere of  $\text{N}_2$  was added Zn (0.25 g, 3.78 mmol) followed by 4-(4-methoxyphenyl)butyl bromide<sup>17</sup> (900 mg, 3.78 mmol) and the mixture stirred overnight at room temperature. The reaction mixture was diluted with EtOAc (100 mL) and extracted with a 17.5% aqueous solution of  $\text{NH}_3$  saturated with  $\text{Na}_2\text{EDTA}$  ( $2 \times 100$  mL) then 1M HCl ( $2 \times 100$  mL),  $\text{H}_2\text{O}$  ( $3 \times 100$  mL) and brine (100 mL). The organic phase was dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure to give **12** (615 mg, >99%) as a colorless which required no further purification. M.p. 55–58 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.02 (d, 4H,  $J$  = 8.6,  $\text{H}_c$ ), 6.75 (d, 4H,  $J$  = 8.6,  $\text{H}_b$ ), 3.72 (s, 6H,  $\text{H}_a$ ), 2.46 (m, 4H,  $\text{H}_d$ ), 1.60 – 1.50 (m, 4H,  $\text{H}_e$ ) 1.35 – 1.26 (m, 8H,  $\text{H}_{f+g}$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 157.5, 135.0, 129.2, 113.6, 55.2, 35.0, 31.74, 29.4, 29.2; LRAPCI-MS:  $m/z$  = 327  $[M+H]^+$ ; HRESI-MS:  $m/z$  = 327.2312 (calcd. for  $\text{C}_{22}\text{H}_{31}\text{O}_2$ , 327.2319).

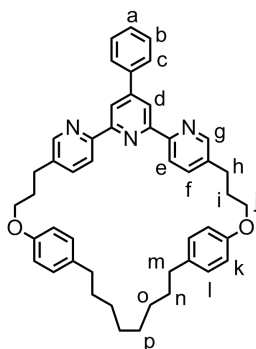


**13**

To a suspension of **12** (326 mg, 1.0 mmol) in  $\text{CHCl}_3$  (0.5 mL), was added trimethylsilyliodide (370  $\mu\text{L}$ , 2.6 mmol) and the resulting solution allowed to stir at 50 °C for 48 h. The reaction mixture was poured into an aqueous 1 M solution of HCl (20 mL) and extracted with  $\text{Et}_2\text{O}$  (4 x 20 mL). The combined organic extracts were



dried ( $\text{MgSO}_4$ ) and the solvent removed under reduced pressure to give **13** (298 mg, >99%) as a colorless solid. M.p. 124–129 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  = 7.03 (d, 4H,  $J$  = 8.4,  $\text{H}_b$ ), 6.74 (d, 4H,  $J$  = 8.4,  $\text{H}_c$ ), 5.31 (s, 2H,  $\text{H}_a$ ), 2.46 (t,  $J$  = 2.4, 2H), 1.60 – 1.49 (m, 4H,  $\text{H}_e$ ), 1.31 – 1.26 (m, 8H,  $\text{H}_{f+g}$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  = 153.1, 135.0, 129.4, 114.9, 34.97, 31.7, 29.4, 29.1; LRAPCI-MS:  $m/z$  = 299.2  $[\text{M}+\text{H}]^+$ ; HRESI-MS:  $m/z$  = 299.1998 (calcd. for  $\text{C}_{20}\text{H}_{27}\text{O}_2$ , 299.2006).



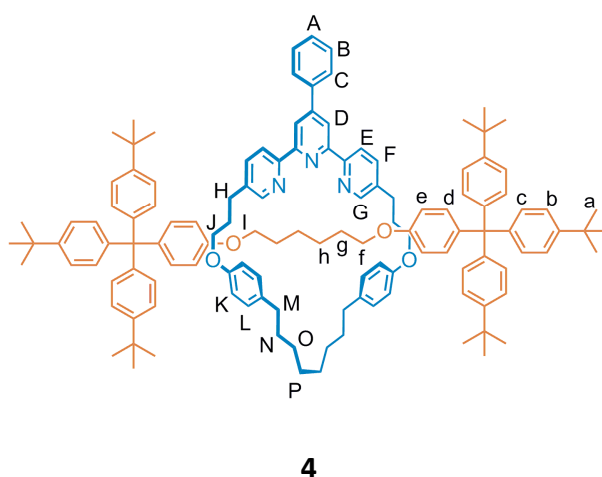
**1**

To a stirred suspension of  $\text{Cs}_2\text{CO}_3$  (0.82 g, 2.51 mmol) in DMF (150 mL) at 60 °C was added a degassed solution of **11** (0.292 g, 0.8 mmol) and **13** (0.369 g, 0.78 mmol) in DMF (80 mL) dropwise over 20 h. After the addition was complete, the reaction mixture was heated and stirred for a further 20 h, its orange color progressively intensifying. The solvent was evaporated under reduced pressure and the crude product was partitioned between  $\text{CH}_2\text{Cl}_2$  (100 mL) and  $\text{H}_2\text{O}$  (100 mL). The phases were separated and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (2 x 100 mL). The combined organic phases were dried ( $\text{MgSO}_4$ ), concentrated under reduced pressure and the resulting brown glassy solid was purified by size exclusion chromatography ( $\text{CH}_2\text{Cl}_2$  as eluent) to give **1** as a colorless powder (300 mg, 60%). M.p. 192–194 °C.  $\delta$  = 8.69 (s, 2H,  $\text{H}_d$ ), 8.58 (d, 2H,  $J$  = 2.0,  $\text{H}_g$ ), 8.50 (d, 2H,  $J$  = 8.0,  $\text{H}_e$ ), 7.91 (dd, 2H,  $J$  = 8.8, 2.0,  $\text{H}_c$ ), 7.58 (dd, 2H,  $J$  = 8.8, 2.0,  $\text{H}_b$ ), 7.53 – 7.45 (m, 3H,  $\text{H}_{a+f}$ ), 7.04 (d, 4H,  $J$  = 7.6,  $\text{H}_i$ ), 6.76 (d, 4H,  $J$  = 8.4,  $\text{H}_k$ ), 3.88 (t, 4H,  $J$  = 6.0,  $\text{H}_j$ ), 2.93 (t, 4H,  $J$  = 7.6,  $\text{H}_n$ ), 2.52 (t, 4H,  $J$  = 7.6,  $\text{H}_m$ ), 2.12 – 2.15 (m, 4H,  $\text{H}_l$ ), 1.56 – 1.53 (m, 2H,  $\text{H}_o$ ), 1.31 – 1.26 (m, 4H,  $\text{H}_o+\text{H}_p$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  156.5, 155.8, 154.2, 150.2, 149.5, 138.6, 137.6, 136.6, 135.1, 129.3, 128.9, 128.9, 127.3, 120.8, 118.4, 114.4, 65.0, 34.9, 31.6, 29.9,

29.0, 28.8, 28.5; LRAPCI-MS  $m/z = 688 [M+H]^+$ ; HRESI-MS:  $m/z = 688.3895$  (calcd. for  $C_{47}H_{50}O_2N_3$ , 688.3898).

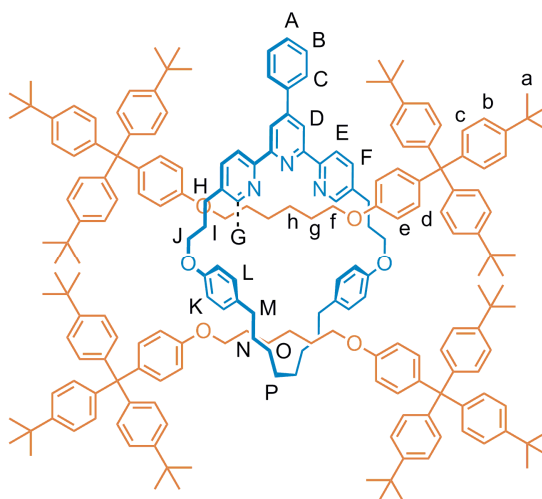
### 2.4.2 General Experimental Procedure for the Synthesis of Rotaxanes

To a solution of terpyridine macrocycle **1** (10 mg, 14.5  $\mu\text{mol}$ ) and  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  (3.45 mg, 14.5  $\mu\text{mol}$ ) in NMP (0.5 mL) under an inert atmosphere of nitrogen was added activated Zn powder and the resulting suspension stirred vigorously for 5 min giving change green/yellow to deep purple. A solution of stoppered bromide **2**<sup>18</sup> in THF (0.5 mL) was then added and the resulting mixture stirred at 60 °C for 18 h. The reaction mixture was diluted with EtOAc (40 mL) and extracted with a 17.5% aqueous solution of  $\text{NH}_3$  saturated with  $\text{Na}_2\text{EDTA}$  ( $2 \times 40$  mL),  $\text{H}_2\text{O}$  ( $3 \times 40$  mL) and brine (40 mL). The organic layer was dried ( $\text{MgSO}_4$ ), the solvent removed under reduced pressure and the resulting residue was purified by size exclusion chromatography ( $\text{CH}_2\text{Cl}_2$  as eluent, see Figure 2.5) to give [2]rotaxane **4**, [3]rotaxane **5** and non-interlocked thread **3**<sup>19</sup> as colorless powders.



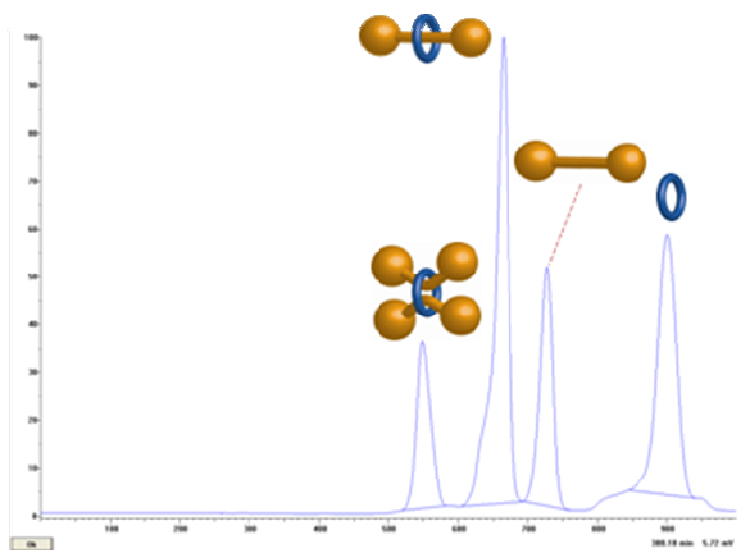
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta = 8.70$  (s, 2H,  $\text{H}_\text{D}$ ), 8.53 (d,  $J = 1.7$ , 2H,  $\text{H}_\text{G}$ ), 8.28 (d,  $J = 8.0$ , 2H,  $\text{H}_\text{E}$ ), 7.85 (d,  $J = 7.3$ , 2H,  $\text{H}_\text{C}$ ), 7.49 – 7.37 (m, 3H,  $\text{H}_{\text{B}+\text{A}}$ ), 7.27 (d,  $J = 1.9$ , 2H,  $\text{H}_\text{F}$ ), 7.22 – 7.14 (m, 12H,  $\text{H}_\text{b}$ ), 7.09 – 7.02 (m, 12H,  $\text{H}_\text{c}$ ), 6.99 – 6.92 (m, 4H,  $\text{H}_\text{d}$ ), 6.87 (d,  $J = 8.6$ , 4H,  $\text{H}_\text{L}$ ), 6.65 (d,  $J = 8.6$ , 4H,  $\text{H}_\text{K}$ ), 6.41 (d,  $J = 9.0$ , 4H,  $\text{H}_\text{e}$ ), 3.78 (t,  $J = 5.9$ , 4H,  $\text{H}_\text{j}$ ),

3.54 (t,  $J = 6.4$ , 4H,  $H_f$ ), 2.92 – 2.78 (m, 4H,  $H_H$ ), 2.39 (t,  $J = 7.4$ , 4H,  $H_M$ ), 2.07 – 1.98 (m, 4H,  $H_I$ ), 1.48 – 1.42 (m, 4H,  $H_g$ ), 1.40 – 1.34 (m, 4H,  $H_N$ ), 1.28 (s, 54H,  $H_a$ ), 1.19 – 1.13 (m, 8H,  $H_{h+o}$ ), 1.11 – 1.07 (m, 4H,  $H_P$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta = 156.8, 156.5, 155.7, 153.9, 151.0, 149.2, 148.2, 144.2, 139.2, 138.5, 137.7, 136.7, 135.1, 132.1, 130.7, 129.3, 128.9, 128.8, 127.3, 124.0, 120.9, 118.3, 114.2, 112.8, 67.3, 64.7, 63.0, 34.9, 34.2, 31.5, 31.4, 29.9, 29.1, 29.1, 28.9, 28.7, 25.8$ ; LRAPCI-MS  $m/z = 1781$   $[\text{M}+\text{H}]^+$ ; HRESI-MS:  $m/z = 1779.1452$  (calcd. for  $\text{C}_{127}\text{H}_{148}\text{O}_4\text{N}_3$ , 1779.1464).



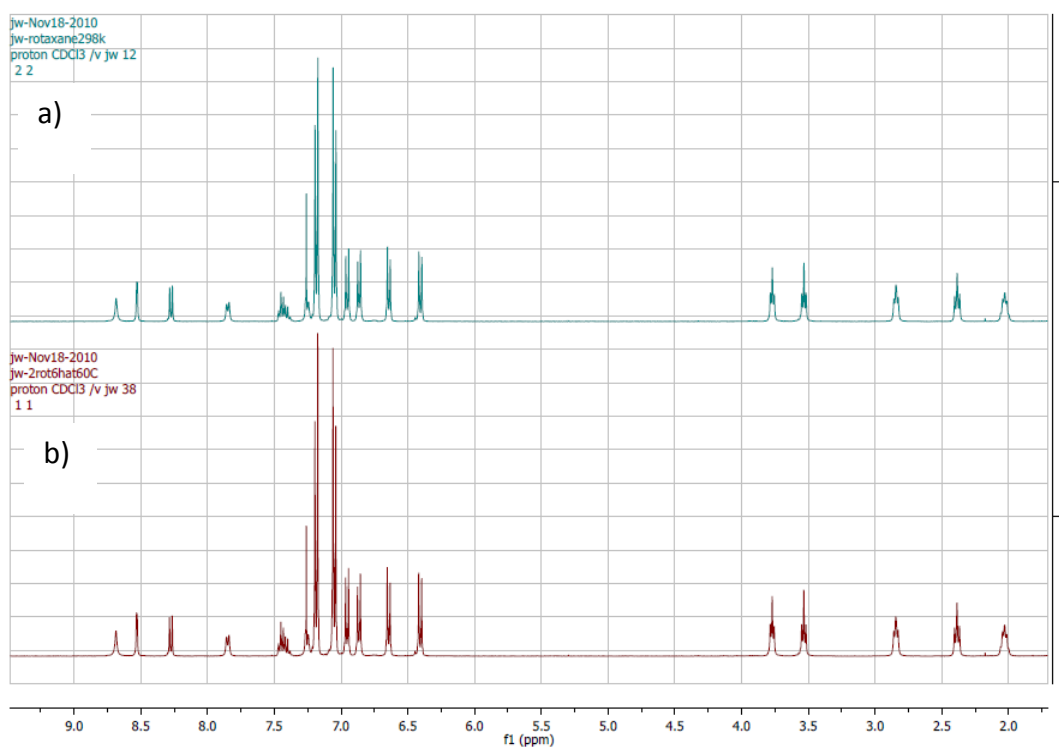
### 5

M.p. 157–159 °C.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta = 8.62$  (br, 4H,  $H_{D+E}$ ), 8.48 (br, 2H,  $G_G$ ), 7.78 (br, 2H,  $H_C$ ), 7.43 – 7.28 (m, 3H,  $H_{A+B}$ ), 7.24 – 7.21 (m, 2H,  $H_F$ ), 7.21 – 7.12 (m, 24H,  $H_b$ ), 7.08 – 6.98 (m, 24H,  $H_c$ ), 6.92 (d,  $J = 8.8$ , 8H,  $H_d$ ), 6.73 (d,  $J = 8.5$ , 4H,  $H_L$ ), 6.48 (d,  $J = 8.6$ , 4H,  $H_K$ ), 6.37 (d,  $J = 8.9$ , 8H,  $H_e$ ), 3.74 (t,  $J = 6.2$ , 4H,  $H_J$ ), 3.22 (t,  $J = 6.6$ , 8H,  $H_f$ ), 2.77 (br, 4H,  $H_H$ ), 2.33 (t,  $J = 7.5$ , 4H,  $H_M$ ), 2.06 – 1.94 (m, 4H,  $H_I$ ), 1.37 – 1.20 (m, 120H,  $H_{a+g+N}$ ), 1.18 – 1.10 (m, 12H,  $H_{h+o}$ ), 0.79 – 0.73 (m, 4H,  $H_P$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta = 156.8, 156.5, 155.8, 153.3, 151.1, 148.3, 144.3, 142.5, 139.2, 139.2, 139.1, 135.4, 135.3, 132.3, 130.9, 129.5, 129.2, 129.1, 127.6, 127.5, 124.4, 124.14, 114.5, 112.9, 67.6, 63.1, 35.8, 34.4, 33.4, 31.6, 31.5, 30.5, 30.30, 29.8, 29.1, 28.5, 25.8$ ; LRESI-MS  $m/z = 2872$   $[\text{M}^{13}\text{C}_2+\text{H}]^+$ ; HRESI-MS:  $m/z = 2871.9148$  (calcd. for  $\text{C}_{205}^{13}\text{C}_2\text{H}_{245}\text{O}_6\text{N}_3$ , 2871.9098).

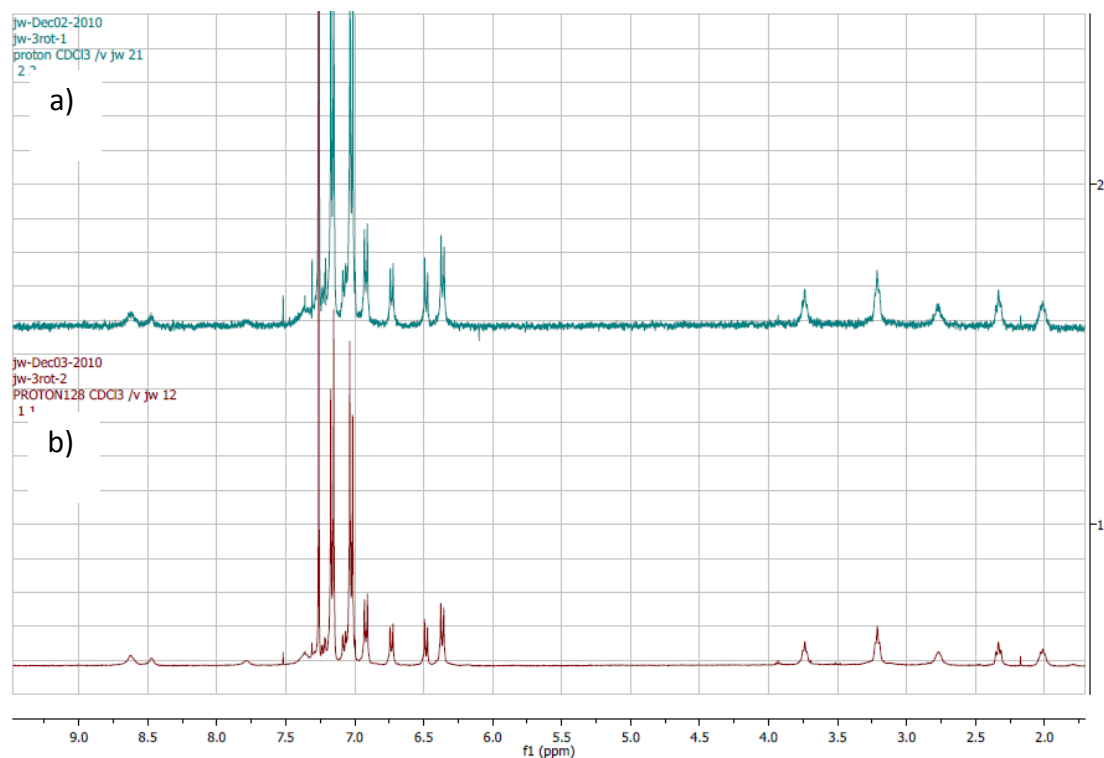


**Figure 2.5.** Representative chromatogram from size exclusion purification of rotaxanes **4** and **5** after a rotaxane forming reaction.

### 2.4.3 Kinetic Studies: Stability of Rotaxanes **4** and **5** at Elevated Temperature



**Figure 2.6.** Partial  $^1\text{H}$  NMR spectra (400 MHz,  $\text{CDCl}_3$ , 298 K) of a) [2]rotaxane **4** b) the same sample after heating at 60 °C for 6 h.



**Figure 2.7.** Partial  $^1\text{H}$  NMR spectra of a) [3]rotaxane **5** b) the same sample after heating at 60 °C for 6 h.

## 2.4.4 Crystal Data and Structure Refinement

### Macrocycle 1

Bond precision: C-C = 0.0112 Å Wavelength=1.54178

Cell: a=11.463(4) b=22.062(8) c=15.984(6)

alpha=90 beta=107.210(7) gamma=90

Temperature: 173 K

	Calculated	Reported
Volume	3861(2)	3861(2)
Space group	P 21	P2(1)
Hall group	P 2yb	P2yb
Moiety formula	C47 H49 N3 O2	C47 H49 N3 O2
Sum formula	C47 H49 N3 O2	C47 H49 N3 O2
Mr	687.89	687.89
Dx, g cm <sup>-3</sup>	1.183	1.183
Z	4	4

Mu (mm-1)	0.558	0.558
F000	1472.0	1472.0
F000	1475.94	
h,k,lmax	13,26,19	13,26,19
Nref	7285[ 14172]	13003
Tmin,Tmax	0.980,0.994	0.758,1.000
Tmin	0.894	

Correction method= MULTI-SCAN

Data completeness= 1.78/0.92 Theta(max)= 68.340

R(reflections)= 0.1077( 8798) wR2(reflections)= 0.3276( 13003)

S = 1.129 Npar= 937

### Macrocyclic complex 1.NiCl<sub>2</sub>

Bond precision: C-C = 0.0366 Å Wavelength=0.71073

Cell: a=48.61(2) b=13.472(6) c=15.627(7)

alpha=90 beta=92.939(10) gamma=90

Temperature: 93 K

	Calculated	Reported
Volume	10220(8)	10220(8)
Space group	C 2/c	C2/c
Hall group	-C 2yc	-C 2yc
Moiety formula	C47 H49 Cl2 N3 Ni O2, C4 H10 O, C3 H7 N O	C47 H49 Cl2 N3 Ni O2, C4 H10 O,C3 H7 N O
Sum formula	C54 H66 Cl2 N4 Ni O4	C54 H66 Cl2 N4 Ni O4
Mr	964.70	964.72
Dx,g cm-3	1.254	1.254
Z	8	8
Mu (mm-1)	0.532	0.532
F000	4096.0	4096.0
F000	4102.41	
h,k,lmax	58,16,18	58,16,18

Nref 9375 9350  
 Tmin,Tmax 0.938,0.995 0.845,1.000  
 Tmin 0.923  
 Correction method= MULTI-SCAN  
 Data completeness= 0.997 Theta(max)= 25.360  
 R(reflections)= 0.3104( 5948) wR2(reflections)= 0.6280( 9350)  
 S = 1.889 Npar= 586

## [2]Rotaxane 4

Bond precision: C-C = 0.0041 Å Wavelength=0.71073

Cell: a=15.632(6) b=19.012(8) c=20.288(9)

alpha=105.149(7) beta=102.006(4) gamma=96.112(6)

Temperature: 93 K

	Calculated	Reported
Volume	5610(4)	5609(4)
Space group	P -1	P-1
Hall group	-P 1	-P 1
Moiety formula	2(C80 H98 O2), 2(C47 H49 N3 O2), 2(C H Cl3), C H Cl2, Cl	C47 H49 N3 O2, C80 H98 O2, 1.5(C H Cl3)
Sum formula	C257 H297 Cl9 N6 O8	C128.50 H148.50 Cl4.50 N3 O4
Mr	3917.06	1958.53
Dx,g cm-3	1.159	1.160
Z	1	2
Mu (mm-1)	0.171	0.172
F000	2098.0	2098.0
F000	2100.05	
h,k,lmax	18,22,24	18,22,24
Nref	20774	20614
Tmin,Tmax	0.966,0.997	0.759,1.000
Tmin	0.966	

Correction method= MULTI-SCAN

Data completeness= 0.992 Theta(max)= 25.460

R(reflections)= 0.2014( 13060) wR2(reflections)= 0.5281( 20614)

S = 1.704 Npar= 1279

### [3]Rotaxane 5

Bond precision: C-C = 0.0078 Å Wavelength=1.54178

Cell: a=14.886(3) b=25.124(6) c=29.790(7)

alpha=91.765(10) beta=100.119(9) gamma=90.483(13)

Temperature: 173 K

	Calculated	Reported
Volume	10962(4)	10962(4)
Space group	P -1	P-1
Hall group	-P 1	?
Moiety formula	2(C <sub>80</sub> H <sub>98</sub> O <sub>2</sub> ), C <sub>47</sub> H <sub>49</sub> N <sub>3</sub> O <sub>2</sub>	C <sub>207</sub> H <sub>245</sub> N <sub>3</sub> O <sub>6</sub> , 10(C H Cl <sub>3</sub> )
Sum formula	C <sub>207</sub> H <sub>245</sub> N <sub>3</sub> O <sub>6</sub>	C <sub>217</sub> H <sub>255</sub> Cl <sub>30</sub> N <sub>3</sub> O <sub>6</sub>
Mr	2871.07	4064.74
Dx,g cm <sup>-3</sup>	0.870	1.231
Z	2	2
Mu (mm <sup>-1</sup> )	0.385	3.817
F <sub>000</sub>	3112.0	4272.0
F <sub>000</sub>	3119.88	
h,k,lmax	17,30,35	17,27,35
Nref	40355	37247
Tmin,Tmax	0.536,0.466	0.731,1.000
Tmin	0.405	

Correction method= MULTI-SCAN

Data completeness= 0.923 Theta(max)= 68.520

R(reflections)= 0.1900( 21402) wR2(reflections)= 0.5084( 37247)

S = 1.731 Npar= 1909



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11. In general free 2,2':6',2''-terpyridine ligands preferentially adopt a *trans-trans* geometry. When acting as a tridentate ligand, rotation around the 2,2'- and 6',2'' bonds occurs to give the coordinating *cis-cis* geometry, see: C. Bazzicalupi, A. Bencini, A. Bianchi, A. Danesi, E. Faggi, C. Giorgi, S. Santarelli, B. Valtancoli, *Coord. Chem. Rev.* **2008**, 252, 1052–1068.
12. An optimized 46% yield of [2]rotaxane was reported in ref (8n) using the bisoxazoline macrocycle and 2.2 equivalents of alkyl bromide at room temperature in DMF. In the present study with the terpyridyl-macrocycle (**1**), the

use of a 1:1 mixture of THF-NMP enabled all of the reactants to be in solution at the start of the reaction. Heating to 60 °C was necessary to allow reactions with >5 equivalents of **2** to reach completion within 18 h. The proportion of interlocked and non-interlocked products was unchanged when the reactions were carried out with DMF as solvent and/or at room temperature (other conditions as for Table 1, entry 2).

13. Two-ring-one-thread [3]rotaxanes have previously been observed as byproducts in Cu-catalyzed azide-alkyne cycloaddition (CuAAC) active metal template reactions, see ref 8d.
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15. A “sheaf” (plural: sheaves) is a bundle of objects held together by a band or other mechanical binder. Familiar examples include the way that wheat, rye and other cereals are traditionally bound with straw or twine after reaping.
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## Chapter 3

# Active Metal Template Synthesis of [2]Catenanes

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## Synopsis

*The synthesis of [2]catenanes by single macrocyclization and double macrocyclization strategies using Cu(I) ions to catalyze covalent bond formation while simultaneously acting as the template for the mechanically interlocked structure is reported. These 'active metal template' strategies employ appropriately functionalized pyridine ether or bipyridine ligands and either the CuAAC 'click' reaction of azides with terminal alkynes or the Cu(I)-mediated Cadiot-Chodkiewicz heterocoupling of an alkyne halide with a terminal alkyne. Using one macrocyclic and one acyclic building block, heterocircuit (the rings are constitutionally different) [2]catenanes are produced via the single macrocyclization route in up to 53% yield by optimizing the reaction conditions and relative stoichiometry of the starting materials. Alternatively, with the active template CuAAC reaction, a single acyclic unit can be used to form a homocircuit (two identical rings) [2]catenane in 46% yield through a one pot, double macrocyclization, procedure. Remarkably, <7% of the corresponding non-interlocked macrocycle is isolated from this reaction, indicating the efficacy of Cu(I) as both a template for the catenane and a catalyst for covalent bond formation in the reaction.*

## Acknowledgements:

The following people are gratefully acknowledged for their contribution to this chapter: Dr. Mark Symes made contributions to writing process. Dr. Paul McGonigal studied the single macrocyclization CuAAC AMT reactions. Most of the synthesis and the investigation were carried out by the autuor. Tao Long repeated synthesizing the building blocks **2** for use. Dr. Symes and Dr. Stephen Goldup made crucial contributions to the project design.

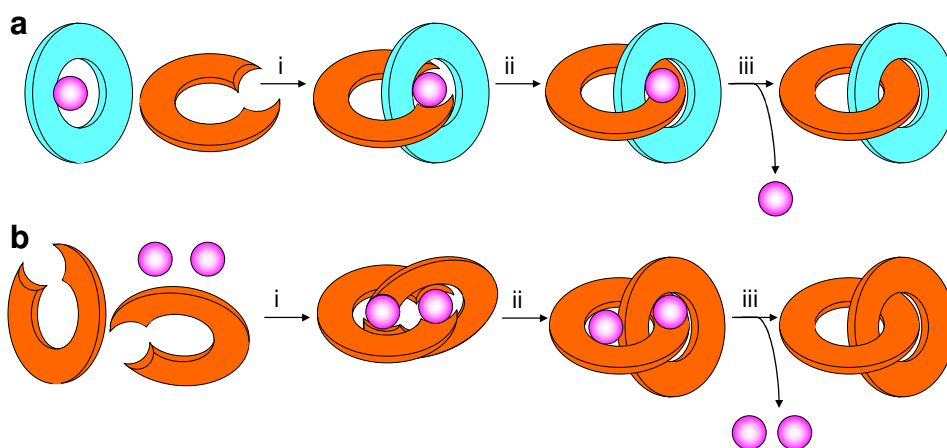
### 3.1 Introduction

The synthesis of catenanes and rotaxanes was revolutionized by the application of template-directed syntheses,<sup>1</sup> in which the components are pre-organized prior to covalent capture of the interlocked architecture. Although a large number of different types of template-directed reactions have been successfully employed to form rotaxanes in threading-followed-by-stoppering strategies,<sup>1a</sup> ‘clipping’ approaches to rotaxanes and catenanes (involving single or double macrocyclization of ligands, directed by the template)<sup>2</sup> are rather more demanding and have only been demonstrated with a small number of different macrocyclization reaction types. Of these, Williamson ether synthesis,<sup>2</sup> the Huisgen-Meldal-Fokin Cu(I)-catalyzed 1,3-cycloaddition of azides with terminal alkynes (the CuAAC ‘click’ reaction),<sup>3,4</sup> amide or ester bond forming reactions,<sup>5</sup> ring-closing metathesis,<sup>6</sup> imine-bond formation<sup>1u,6f,7</sup> and metal-ligand coordination<sup>8</sup> are the most commonly used. The effectiveness of these reactions for catenane synthesis lies in their reactive end-groups being sufficiently stable in solution to react overwhelmingly in the desired fashion even when accessing the required reaction geometry is a rare event (as it is for the cyclization of large rings), and hence give predominantly macrocyclic products under high dilution. The yield of catenane versus non-interlocked macrocycle then depends on how effectively the template pre-organizes the ring-closing reaction to take place while one component is threaded through the cavity of the other.

We recently developed<sup>9</sup> an approach to rotaxane synthesis in which a metal ion ligated endotopically within a macrocycle mediates bond formation between two suitably functionalized building blocks through the macrocycle cavity to assemble the thread. This ‘active metal template’ strategy<sup>9</sup> takes inspiration from ligand couplings employed in transition metal catalysis and opens up a broad range of metal-mediated bond formations for possible use in the synthesis of rotaxanes – the requirement being that the key bond-forming reaction can be directed by the catalyst to proceed through the macrocyclic cavity rather than external to it. Such active metal template processes, where a single species acts as both the template and the catalyst for covalent bond formation, clearly also offer potential for the synthesis of catenanes (Figure 1). Using a metal ion to simultaneously bind to and



activate the tethered ends of an acyclic building block to react through the cavity of a macrocycle could lead to reactions with unstable intermediates that would otherwise not lead to interlocked products being used for possible catenane-forming reactions. Active template processes also offer the possibility of traceless assembly<sup>9i</sup> (as the coordinating functional groups are often chemically changed during the reaction into non-coordinating elements) and could be used to prepare catenanes containing multiple rings or having only very weak residual intercomponent interactions – molecules that are often difficult or impossible to achieve with standard template-directed approaches. Here we report on the application of the active metal template concept to catenane synthesis using both single macrocyclization and double macrocyclization strategies. Heterocircuit (the rings are different) and homocircuit (the rings are the same) [2]catenanes are assembled using appropriately functionalized bidentate pyridine ether or bipyridine ligands and either the Cu(I)-catalyzed CuAAC reaction or the Cu(I)-mediated Cadiot-Chodkiewicz<sup>10</sup> heterocoupling of an alkynyl halide and a terminal alkyne.

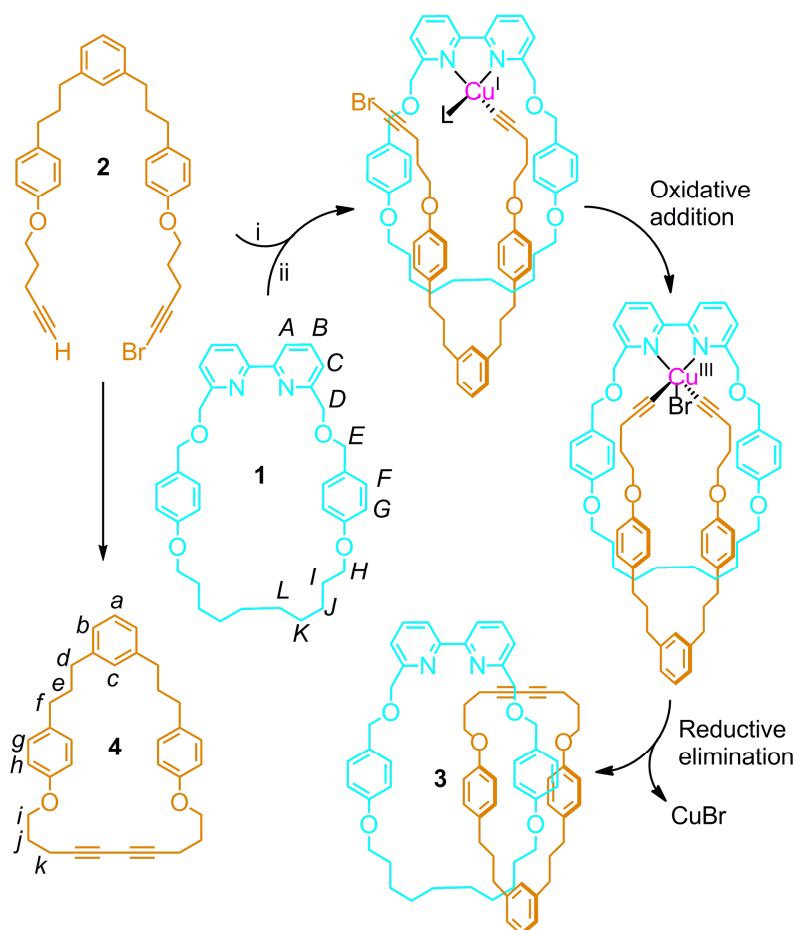


**Figure 3.1.** The active metal template approach to catenane synthesis. (a) Single macrocyclization route: (i) Template assembly of a macrocyclic ligand and an acyclic ligand about the metal ion (shown in pink) is followed, (ii), by a covalent-bond forming reaction between the end groups of the acyclic ligand, catalyzed by the metal ion, through the cavity of the macrocycle. (iii) Decomplexation affords the metal-free [2]catenane. (b) Double macrocyclization route: (i) Template assembly of the acyclic ligands about one or more metal ions is followed by (ii) successive or simultaneous macrocyclization reactions. (iii) Decomplexation affords the metal-free homocircuit (both macrocycles are the same) [2]catenane. The two routes are analogous to the single and double macrocyclization strategies introduced by Sauvage for the synthesis of catenanes by 'passive' metal template methods.<sup>2</sup>

## 3.2 Results and Discussion

### 3.2.1 Active metal template [2]catenane synthesis using the Cadiot-Chodkiewicz reaction

We initially investigated a modified Cadiot-Chodkiewicz coupling<sup>11</sup> of a bromoalkyne with a terminal alkyne mediated by a Cu<sup>I</sup> complex of bidentate bipyridyl macrocycle **1**,<sup>9d</sup> due to its efficacy in active template rotaxane-forming reactions.<sup>9g</sup> Acyclic unit **2**, which has no potential metal-coordinating sites other than the terminal alkyne and bromoalkyne reactive functional groups, was treated with LiHMDS (LiN(SiMe<sub>3</sub>)<sub>2</sub>) at -78 °C then added to a solution of macrocycle **1** and CuI in THF, and the resulting mixture stirred for 4 days at room temperature (Scheme 1), a procedure similar to that used successfully<sup>9g</sup> for rotaxane formation. However, little of the desired catenane product (**3**) was observed and only a small amount of **2** consumed under these conditions. Increasing the reaction concentration, raising the reaction temperature to 80 °C and employing a fivefold excess of **2** ultimately gave [2]catenane **3** in 21% yield. The proposed mechanism for the active metal template Cadiot-Chodkiewicz catenane synthesis is shown in Scheme 1.<sup>12</sup> The modest yield illustrates how the catenane-forming reaction, in which the reactive end groups must be tethered together, is much more demanding in terms of conformational requirements of the ligands, and probably steric effects, than the equivalent rotaxane-forming reaction (for which non-tethered functional groups are reacted through the macrocycle cavity to form the interlocked thread). The yield of catenane also suffers because the bromoalkyne moiety is present during treatment of the terminal alkyne of **2** with LiHMDS, prior to transmetallation with copper. This leads to some decomposition of the alkyne halide, whereas in the corresponding rotaxane-forming reactions, the terminal alkyne could be treated with LiHMDS and transmetallated with copper before the alkyne halide was added to the reaction mixture.

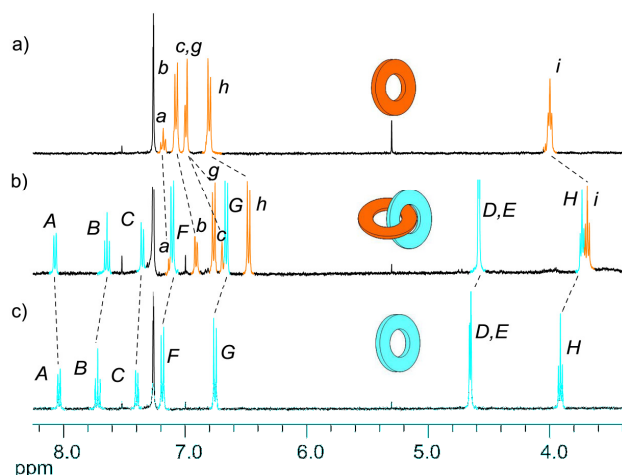


**Scheme 3.1.** Active Metal Template Cadiot-Chodkiewicz Synthesis of [2]Catenane **3** from Bipyridyl Macrocycle **1** and Alkyne-Bromoalkyne **2**<sup>a</sup>

<sup>a</sup>Reagents and conditions: (i) LiHMDS, THF, -78 °C; (ii) CuI (1 equiv.), 5 equiv. of **2**, 80 °C, 72 h, 21 % (over two steps). L = I, Br or THF.

As a heterocircuit catenane (the two rings are different), the interlocked nature of **3** was apparent from both mass spectrometry ( $m/z$  of the molecular ion) and  $^1\text{H}$  NMR spectroscopy. The  $^1\text{H}$  NMR spectrum of [2]catenane **3** in  $\text{CDCl}_3$  (Figure 3.2b) displays upfield shifts of nearly all of the signals with respect to those of the non-interlocked components (Figures 3.2a and 2c). Such shielding is typical of interlocked architectures in which the aromatic rings of one component are face-on to another component, and is most conspicuous for  $\text{H}_F$ ,  $\text{H}_G$  and  $\text{H}_H$  of macrocycle **1** and  $\text{H}_c$ ,  $\text{H}_h$  and  $\text{H}_i$  of macrocycle **4**. The ubiquity of the upfield shifts implies that the two rings are largely free to rotate with respect to one another, as might be expected in a

system where there are no strong intercomponent interactions to stabilize a particular co-conformation.



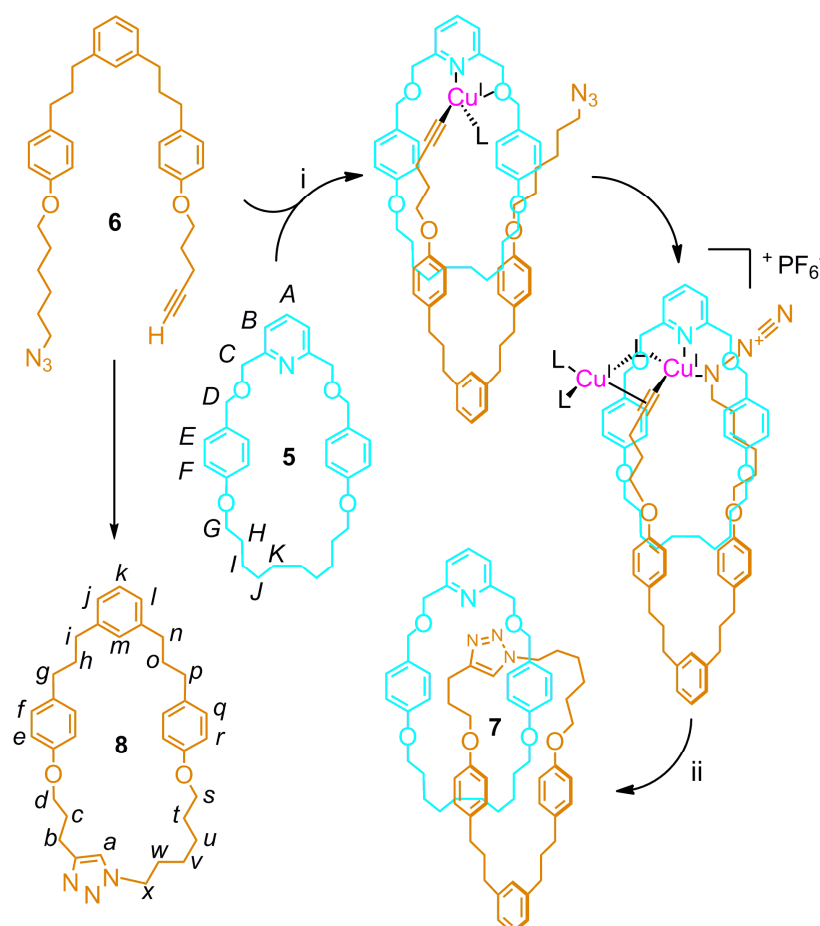
**Figure 3.2.** Partial  $^1\text{H}$  NMR spectra (400 MHz,  $\text{CDCl}_3$ , 300 K) of (a) bisacetylene macrocycle **4**, (b) [2]catenane **3**, (c) bipyridine macrocycle **1**. The assignments correspond to the lettering shown in Scheme 1.

### 3.2.2 Active metal template [2]catenane synthesis using the CuAAC

#### ‘click’ reaction: Single macrocyclization strategy

The qualified success of the catenane-forming active template Cadiot-Chodkiewicz reaction prompted us to try using the CuAAC ‘click’ reaction to form [2]catenanes (Scheme 2, Table 1), a reaction that had also been previously successfully applied to the active template synthesis of rotaxanes<sup>9a,d</sup> and passive template syntheses of both rotaxanes<sup>1t,13</sup> and catenanes<sup>4</sup>. When an equimolar mixture of macrocycle **5**,<sup>14</sup>  $[\text{Cu}(\text{CH}_3\text{CN})_4](\text{PF}_6)$ , and the acyclic azide-alkyne unit **6** in dichloromethane was stirred for 24 hours at room temperature a low conversion to triazole products was observed with only trace amounts of catenane apparent in the  $^1\text{H}$  NMR analysis of the crude reaction mixture (Table 1, entry 1). Changing the solvent to 1,2-dichloroethane and raising the temperature to 80 °C afforded [2]catenane **7** in 16% yield with near complete conversion of **6** to triazole products (Table 1, entry 2). Finally, by increasing the number of equivalents of **6** relative to **5** and running the

reaction at greater dilution (which required extended reaction times) the yield of catenane **7** was increased to a pleasing 53% (Table 1, entry 4). Isolation of the metal-free catenane was facilitated by washing the crude product mixture with a basic EDTA solution.



**Scheme 3.2.** Single Macrocyclization Strategy Active Metal Template CuAAC Synthesis of [2]Catenane **7** from Pyridyl Macrocycle **5** and Azide-Alkyne **6**.<sup>a</sup>

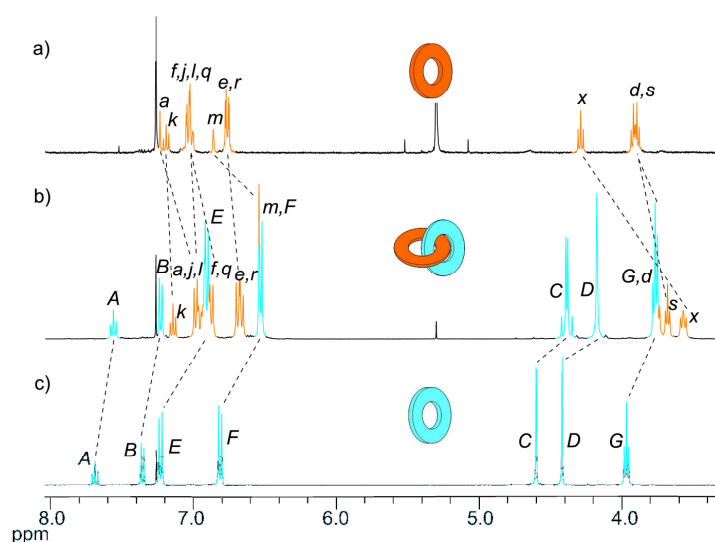
<sup>a</sup>Reagents and conditions: (i)  $[Cu(CH_3CN)_4](PF_6)$ ,  $CH_2Cl_2$  or  $C_2H_4Cl_2$ ; (ii) EDTA,  $NH_3(aq)$ . L =  $CH_3CN$ , alkyne, azide or donor atom from another molecule. For the effect of conditions and reagent stoichiometry on the reaction yield, see Table 3.1.

**Table 3.1.** Influence of Reaction Conditions and Reagent Stoichiometry on the Single Macrocyclization Strategy Active Metal Template CuAAC Synthesis of [2]Catenanes **7** and **9** (Schemes 2 and 3).<sup>a</sup>

Entry	Macrocycle (concentration)	Equiv. 6	T / °C	Time / h	Conversion to triazole products (%)	Yield (%) of [2]catenane 5→7  1→9
1 <sup>a</sup>	5 (6.5 mM)	1	RT	24	15 <sup>b</sup>	<5 <sup>b</sup>
2	5 (6.5 mM)	1	80	96	90	16
3	5 (6.5 mM)	5	80	240	>98	25
4	5 (1.25 mM)	5	80	288	>98	53
5	1 (1 mM)	5	80	500	50	50
6	1 (5 mM)	5	80	170	>98	49

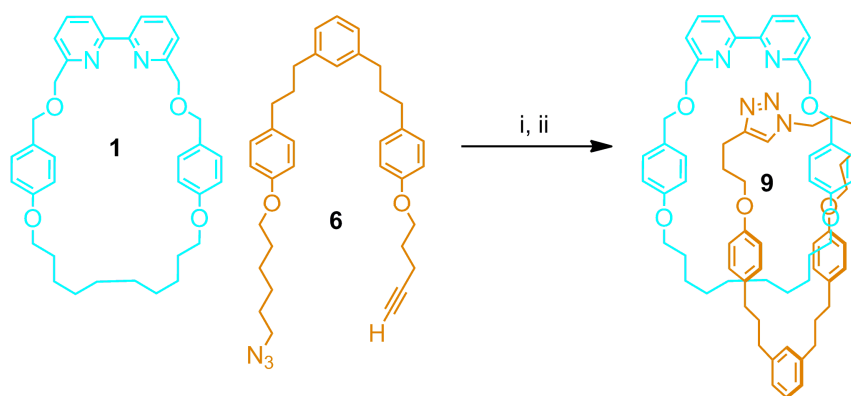
<sup>a</sup> One equivalent of [Cu(CH<sub>3</sub>CN)<sub>4</sub>](PF<sub>6</sub>) was used relative to the macrocycle (1 or 5). All reactions were carried out in C<sub>2</sub>H<sub>4</sub>Cl<sub>2</sub>, except entry 1 (CH<sub>2</sub>Cl<sub>2</sub>). <sup>b</sup> Yield estimated by <sup>1</sup>H NMR.

The <sup>1</sup>H NMR spectrum of catenane **7** (Figure 3.3b) shows significant upfield shifts of various signals (H<sub>x</sub> ~0.6 ppm, H<sub>m</sub> ~0.4 ppm, H<sub>E</sub> ~0.3 ppm and H<sub>F</sub> ~0.3 ppm) with respect to the components (Figure 3.3a and 3c), consistent with its interlocked architecture. Interestingly, signals corresponding to H<sub>C</sub> appear as an AB system, indicating that the two faces of the pyridyl macrocycle are inequivalent. This is a result of the triazole group making the ring threaded through the pyridyl macrocycle inherently unsymmetrical. The chemical shift of H<sub>a</sub> of the triazole group suggests it may form a C-H...N hydrogen bond<sup>15</sup> with the pyridine nitrogen atom of the other macrocycle.



**Figure 3.3.** Partial  $^1\text{H}$  NMR spectra (400 MHz,  $\text{CDCl}_3$ , 300 K) of (a) triazole macrocycle **8**, (b) [2]catenane **7**, (c) pyridine macrocycle **5**. The assignments correspond to the lettering shown in Scheme 2.

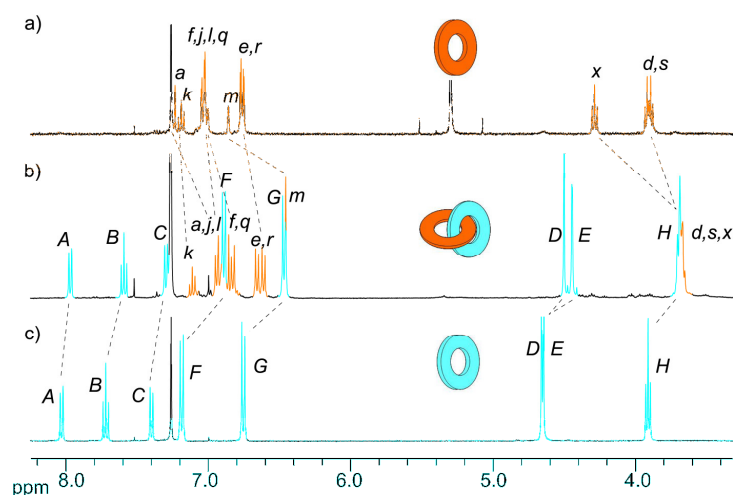
Both pyridyl and bipyridyl macrocycles have been found to undergo efficient active template rotaxane assembly with the CuAAC reaction,<sup>9d</sup> although the kinetics of the reactions are very different (the bipyridyl macrocycle reaction is considerably slower) as a result of the reactions proceeding through different types of intermediates. The same trend was seen with the active template catenane-forming reaction (Scheme 3.3 and Table 3.1, entries 5 and 6). Although good yields (49-50%) of [2]catenane **9** could be obtained, they required long reaction times (7-21 days) at 80 °C and/or higher reaction concentrations. It is testimony to the very specific reaction preferences of the azide and alkyne functional groups under Cu(I) catalysis that they survive for so long without undergoing side reactions until the apparently very rare event of the groups being in just the right position to react to form catenane occurs.



**Scheme 3.3.** Single Macrocyclization Strategy Active Metal Template CuAAC Synthesis of [2]Catenane **9** from Bipyridyl Macrocycle **1** and Azide-Alkyne **6**.<sup>a</sup>

<sup>a</sup>Reagents and conditions: (i)  $[\text{Cu}(\text{CH}_3\text{CN})_4](\text{PF}_6)_3$ ,  $\text{C}_2\text{H}_4\text{Cl}_2$ , 80 °C, 7-21 d. (ii) EDTA,  $\text{NH}_3(\text{aq})$ , 49-50% (over two steps). For the effect of concentration on the time of reaction, see Table 1.

The  $^1\text{H}$  NMR spectrum of catenane **9** (Figure 3.4b) again shows upfield shifts of most of its signals with respect to its non-interlocked components (Figures 3.4a and 4c). Signals  $\text{H}_F$  and  $\text{H}_G$  of bipyridine macrocycle **1** are each shifted by  $\sim 0.2$  ppm, consistent with  $\pi$ - $\pi$  stacking between the aromatic rings to which  $\text{H}_F$  and  $\text{H}_G$  are attached and the aromatic rings of macrocycle **8**. As in catenane **7** the signals corresponding to  $\text{H}_E$  appear as an AB system although this is less pronounced than in the pyridine macrocycle-derived catenane.

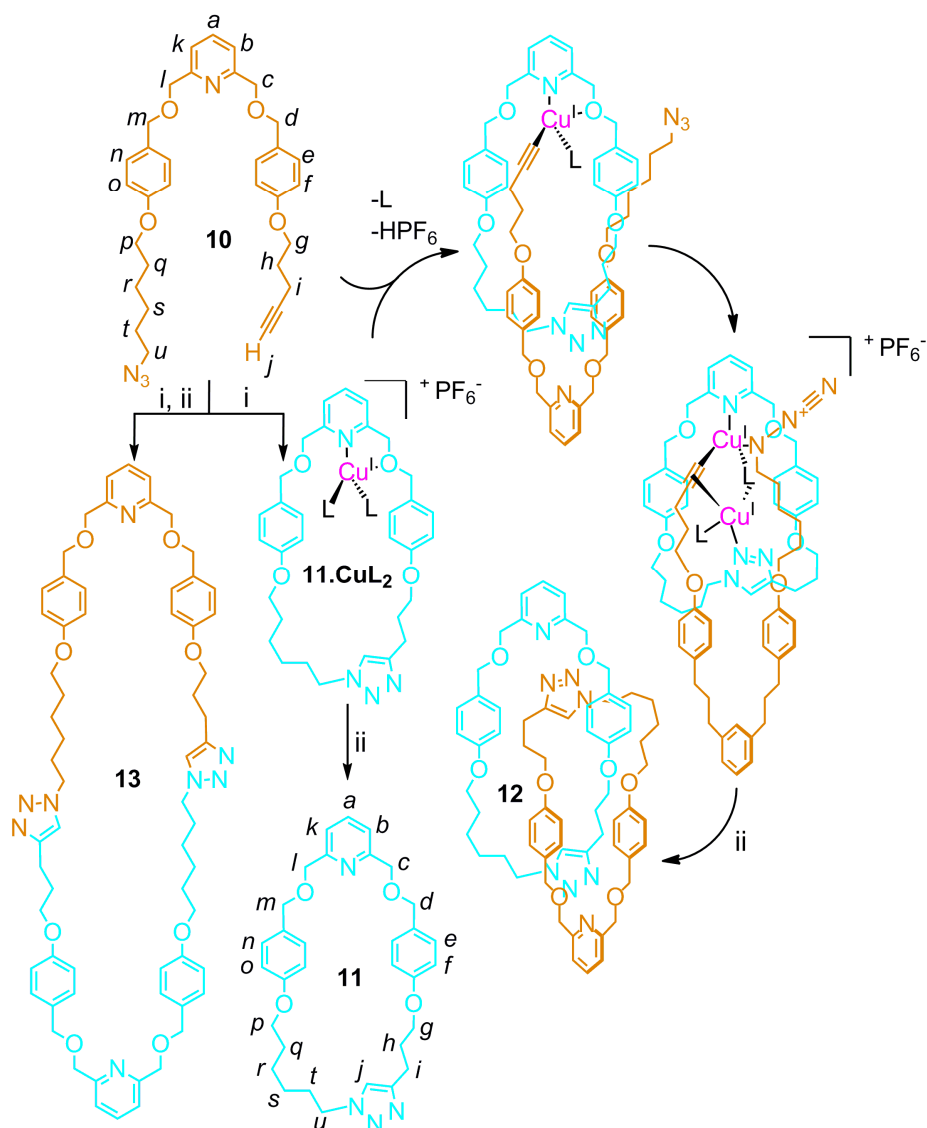


**Figure 3.4.** Partial  $^1\text{H}$  NMR spectra (400 MHz,  $\text{CDCl}_3$ , 300 K) of (a) triazole macrocycle **8**, (b) [2]catenane **9**, (c) bipyridine macrocycle **1**. The assignments correspond to the lettering indicated for macrocycles **1** and **8** in Schemes 1 and 2 respectively.



### **3.2.3 Active metal template [2]catenane synthesis using the CuAAC ‘click’ reaction: Double macrocyclization of two identical acyclic building blocks**

The active template reactions investigated so far (Schemes 3.1-3.3) featured a preformed macrocycle as one of the components and involved a single macrocyclization step (Figure 3.1a) leading to heterocircuit catenanes. We were interested to see whether it would be possible to extend this concept to an active template double macrocyclization strategy (Figure 3.1b) in which a homocircuit (both interlocked rings constitutionally identical) [2]catenane was assembled in one pot by two successive macrocyclization reactions (the final one, at least, having to be templated by the catalyst) of a single type of building block (Scheme 3.4).



**Scheme 3.4.** Double Macrocyclization Strategy Active Metal Template CuAAC Synthesis of [2]Catenane **12** from Azide-Alkyne **10**.<sup>a</sup>

<sup>a</sup>Reagents and conditions: (i)  $[Cu(CH_3CN)_4](PF_6)$ ,  $C_2H_4Cl_2$ ,  $80^\circ C$ , 5 d. (ii) EDTA,  $NH_{3(aq)}$ .  $L = CH_3CN$ , alkyne, azide or donor atom from another molecule. For the effect of concentration on catenane yield, see Table 2.

Ligand **10** incorporates the terminal alkyne and azide groups necessary for the CuAAC reaction, together with a pyridine group for coordination to a Cu ion catalyzing the ring closure of another molecule of **10**. The covalent framework of the ligand was chosen to mimic macrocycle **5** and acyclic unit **6** which combine

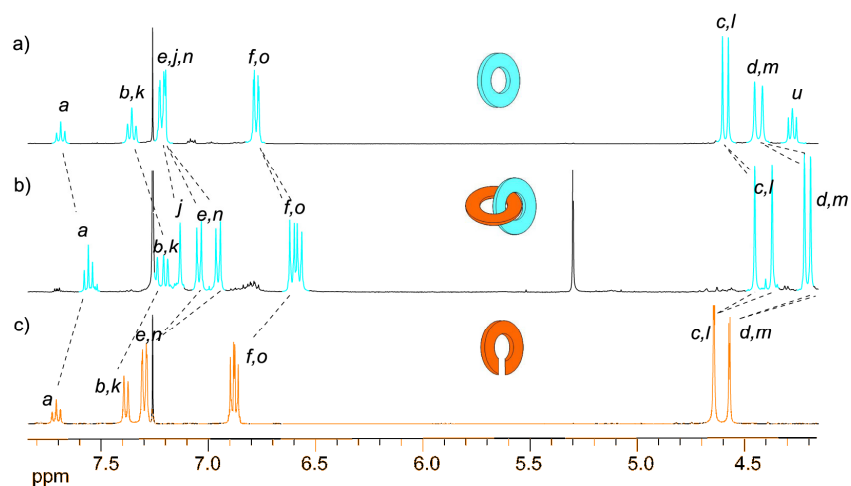
effectively to give catenane in the single macrocyclization active template CuAAC reaction (Scheme 3.2).

Building block **10** was dissolved in  $\text{C}_2\text{H}_4\text{Cl}_2$  with half an equivalent of  $[\text{Cu}(\text{CH}_3\text{CN})_4](\text{PF}_6)$  and the solution heated at  $80\text{ }^\circ\text{C}$  for five days (Scheme 3.4). The yield of [2]catenane proved to be highly dependent on the reaction concentration (Table 3.2), presumably a reflection of the delicate balance between various types of coordination complexes that can give rise to oligomers, non-interlocked macrocycles or catenane. Carrying out the reaction at an initial  $0.3\text{ mM}$  concentration of **10** gave a remarkable 46% yield of metal-free [2]catenane **12**, isolated after work up with a basic EDTA solution and purification by column chromatography. Very little (<7%) of non-interlocked macrocycles **11** and **13** were isolated from the reactions reported in Table 3.2 entries 4 and 5. It is intriguing that even at these relatively low concentrations the double macrocyclization reaction is more selective for the [2]catenane than the corresponding single macrocyclization employing pyridine macrocycle **5** and one equivalent of the acyclic azide-alkyne building block **6** (Scheme 3.2 and Table 1, entry 2). A possible explanation could be that the second Cu(I) ion involved in the mechanism of these reactions<sup>3,9d</sup> becomes coordinated to the triazole nitrogen of macrocycle **11**, resulting in a reaction geometry in which interlocking is significantly enhanced, as shown in Scheme 4. As the two Cu(I) centers are linked *via* both a bridging ligand, L, and coordination to the alkyne, the azide is forced to approach the reactive center through the cavity of macrocycle **11** in order for the CuAAC reaction to occur, leading predominantly to catenane.

**Table 3.2.** Influence of Concentration on the Double Macrocyclization Strategy Active Metal Template CuAAC Synthesis of [2]Catenane **12** (Scheme 4). Half an equivalent of  $[\text{Cu}(\text{CH}_3\text{CN})_4](\text{PF}_6)$  was used relative to **10**. All reactions were performed in  $\text{C}_2\text{H}_4\text{Cl}_2$  at 80 °C over 120 h.

Entry	[ <b>10</b> ] (mM)	Conversion to triazole products (%)	Ratio catenane <b>12</b> : macrocycles <b>11</b> and <b>13</b>	Yield of [2]catenane <b>10</b> → <b>12</b> (%)
<b>1</b>	15	>98	2:3	8
<b>2</b>	6	>98	2:3	16
<b>3</b>	3	>98	5:2	25
<b>4</b>	1	>98	3:1	30
<b>5</b>	0.3	>98	7:1	46
<b>6</b>	0.08	65	1:1	40
<b>7</b>	0.03	25	1:6	6

The structure of [2]catenane **12** was confirmed by mass spectrometry (fragmentation and MS-MS studies) and  $^1\text{H}$  NMR spectroscopy. The  $^1\text{H}$  NMR spectrum of catenane **12** in  $\text{CDCl}_3$  is shown in Figure 5b. The upfield shifts of the signals compared to macrocycle **11** (Figure 3.5a) and building block **10** (Figure 3.5c) show the same general trends found in the heterocircuit catenane produced by the single macrocyclization active template CuAAC reaction, **7** (Figure 3.3).



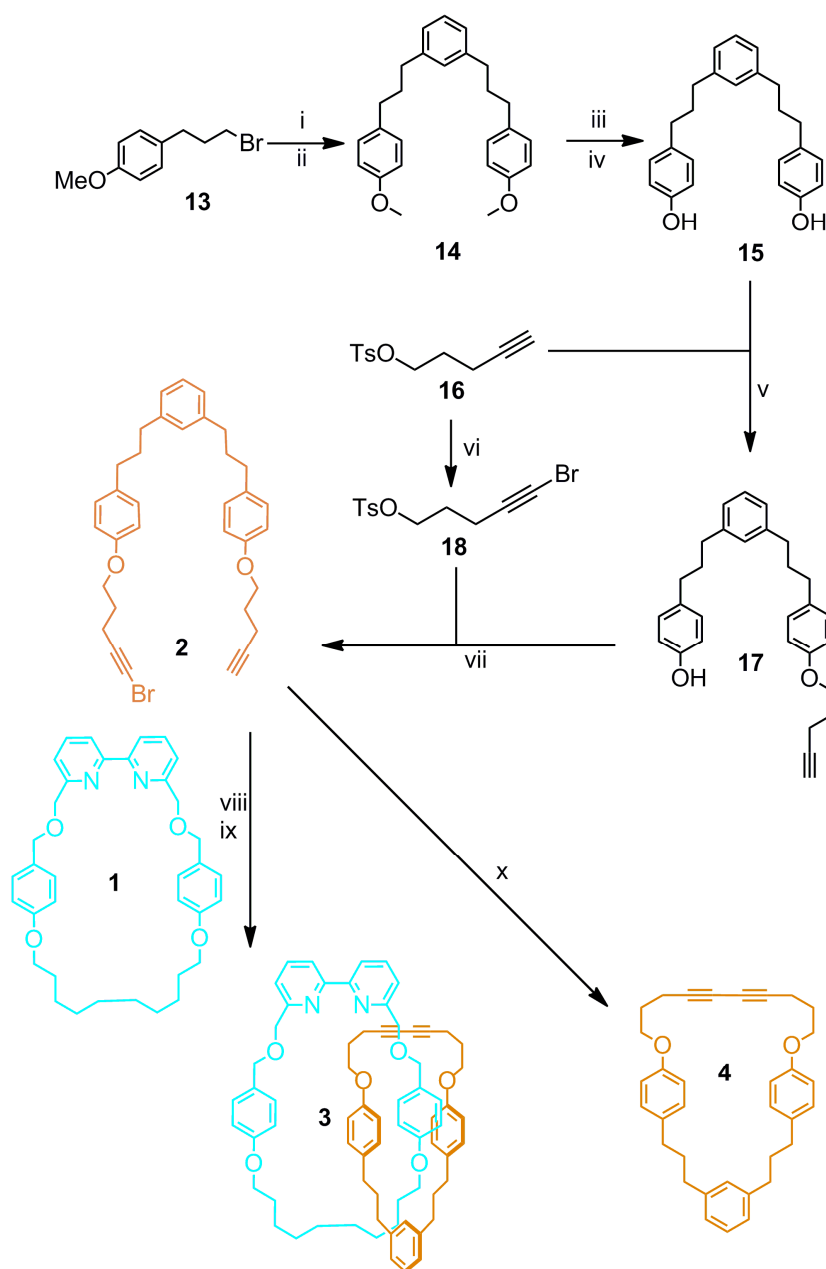
**Figure 3.5.** Partial  $^1\text{H}$  NMR spectra (400 MHz,  $\text{CDCl}_3$ , 300 K) of (a) macrocycle **11**, (b) [2]catenane **12**, (c) azide-alkyne building block **10**. The assignments correspond to the lettering shown in Scheme 4.

### 3.3 Conclusions

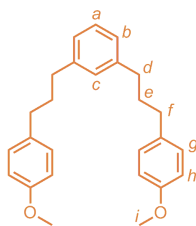
The active template concept developed for rotaxanes can be successfully extended to the more demanding requirements of catenane synthesis. Heterocircuit [2]catenanes were prepared in 21-53% yields through Cu(I)-mediated active template single macrocyclization strategies employing the Cadiot-Chodkiewicz (forming a symmetrical bisacetylene-containing macrocycle) or CuAAC ‘click’ reaction (forming an unsymmetrical triazole-containing macrocycle) and preformed monodentate or bidentate macrocyclic ligands. The CuAAC reaction could also be used to assemble homocircuit [2]catenanes from a single type of acyclic building block in a one pot procedure in up to 46% yield, a remarkable catalytic assembly reaction notable for its selectivity for the interlocked architecture over non-interlocked macrocyclic products. The application of such strategies to higher order interlocked structures is currently under investigation in our laboratory.

### 3.4 Experimental Section

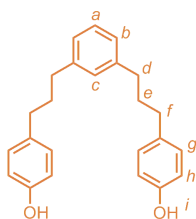
#### 3.4.1. Experimental Procedures



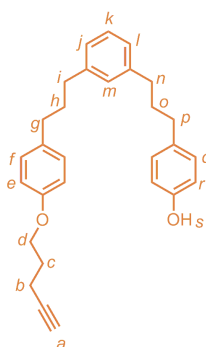
**Scheme 3.5.** (i) Zn, I<sub>2</sub>, NMP, RT → 80 °C, 4 h; (ii) 1,3-dibromobenzene, PEPPSI, LiBr, THF, RT, 2h, 70% (over two steps); (iii) BBr<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C → RT, 2h; (iv) H<sub>2</sub>O, RT, 10 min, 99% (over two steps); (v) K<sub>2</sub>CO<sub>3</sub>, DMF, 80 °C, 18 h, 42%; (vi) NBS, AgNO<sub>3</sub>, acetone, RT, 2 h, 95%; (vii) Cs<sub>2</sub>CO<sub>3</sub>, DMF, 100 °C, 18 h, 93%; (viii) LiHMDS, THF, -78 °C, 30 mins; (ix) Cul, THF, -78 °C → RT, 72 h, 21%; (x) LiHMDS, THF, -78 °C, 30 mins; (xi) Cul, THF, -78 °C → RT, 7 days, 12%.

**14**

To a stirred suspension of Zn (0.49 g, 7.5 mmol, 3.5 eq.) in N-methyl-2-pyrrolidone (NMP) (5 mL) at RT was added I<sub>2</sub> (64 mg, 0.25 mmol, 0.1 eq.) and the mixture stirred until the color due to the iodine had disappeared (approximately 2 minutes). **13** (1.1 g, 4.8 mmol, 2.2 eq.) was added and the reaction mixture was heated at 80 °C for 4 h. After this time, the reaction mixture was cooled to RT and transferred to a flask containing LiBr (0.87 g, 10 mmol, 5 eq.), 1,5-dibromobenzene (0.51 g, 2.1 mmol, 1.0 eq.) and PEPPSI<sup>20</sup> (34 mg, 50 μmol, 0.03 eq.) dissolved in THF (5 mL). The reaction mixture was stirred for 2 h at RT, and then quenched with 1 M HCl (20 mL). The reaction was then extracted with diethyl ether (3 × 50 mL) and the combined organic layers washed with brine (50 mL), dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Purification by flash column chromatography on silica (petroleum ether:ethyl acetate 15:1) yielded the title compound **14** as a colorless oil (0.56 g, yield = 70%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.18 (t, J = 7.6, 1H, H<sub>a</sub>), 7.10 (d, J = 7.6, 4H, H<sub>g</sub>), 7.02-6.99 (m, 3H, H<sub>b+c</sub>), 6.83 (d, J = 7.6, 4H, H<sub>h</sub>), 3.79 (s, 6H, H<sub>i</sub>), 2.64-2.56 (m, 8H, H<sub>d+f</sub>), 1.96-1.88 (m, 4H, H<sub>e</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 157.7, 142.3, 134.4, 129.3, 128.6, 128.2, 125.8, 113.7, 55.3, 35.4, 34.6, 33.2. LRESI-MS: m/z = 375 [M+H]<sup>+</sup>. HRESI-MS: m/z = 392.2565 [M+NH<sub>4</sub>]<sup>+</sup> (calcd. for C<sub>26</sub>H<sub>34</sub>O<sub>2</sub>N, 392.2584 [M+NH<sub>4</sub>]<sup>+</sup>).

**15**

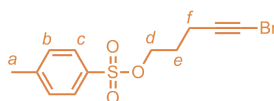
To a solution of compound **14** (0.28 g, 0.75 mmol, 1 eq.) in  $\text{CH}_2\text{Cl}_2$  (3 mL) at  $-78^\circ\text{C}$  was added  $\text{BBr}_3$  (1.1 g, 0.43 mL, 4.5 mmol, 6 eq.) and the reaction stirred at RT for 2 h. After this time, the reaction was quenched with distilled water and the volume of solvent reduced. Filtration gave diphenol **15** as a colorless solid, m.p.  $62\text{--}64^\circ\text{C}$  (0.26 g, yield = 99%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.19 (t,  $J$  = 7.6, 1H,  $\text{H}_a$ ), 7.05 (d,  $J$  = 8.4, 4H,  $\text{H}_g$ ), 7.01–6.97 (m, 3H,  $\text{H}_{b+c}$ ), 6.74 (d,  $J$  = 8.4, 4H,  $\text{H}_h$ ), 4.54 (s, 2H,  $\text{H}_i$ ), 2.62–2.56 (m, 8H,  $\text{H}_{d+f}$ ), 1.94–1.86 (m, 4H,  $\text{H}_e$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 153.5, 142.3, 134.6, 129.5, 128.6, 128.2, 125.8, 115.1, 35.3, 34.6, 33.2. LRESI-MS:  $m/z$  = 345  $[\text{M-H}]^-$ . HRESI-MS:  $m/z$  = 345.1857  $[\text{M-H}]^-$  (calcd. for  $\text{C}_{24}\text{H}_{25}\text{O}_2$ , 345.1860  $[\text{M-H}]^-$ ).

**17**

To a solution of diphenol **15** (2.2 g, 6.3 mmol, 1 eq.) and **16**<sup>16</sup> (1.5 g, 6.3 mmol, 1 eq.) in DMF (13 mL) was added  $\text{K}_2\text{CO}_3$  (1.8 g, 13 mmol, 2 eq.) and the suspension was heated at  $80^\circ\text{C}$  for 18 h. After cooling, the solution was then quenched with 1 M HCl (20 mL), extracted into diethyl ether ( $3 \times 50$  mL) and the combined organic extracts washed with brine (50 mL). The organic layer was separated, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The resulting crude oil was then purified by column chromatography on silica ( $\text{CH}_2\text{Cl}_2$ :ethyl acetate 20:1) to yield **17** as a colorless oil (1.1 g, yield = 42%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.21 (t,  $J$  = 7.6, 1H,  $\text{H}_k$ ), 7.11 (d,  $J$  = 8.8, 2H,  $\text{H}_f$ ), 7.06 (d,  $J$  = 8.4, 2H,  $\text{H}_q$ ), 7.03–7.01 (m, 3H,  $\text{H}_{j+l+m}$ ), 6.85 (d,  $J$  = 8.8, 2H,  $\text{H}_e$ ), 6.76 (d,  $J$  = 8.4, 2H,  $\text{H}_r$ ), 4.90 (s, 1H,  $\text{H}_s$ ), 4.06 (t,  $J$  = 6.0, 2H,  $\text{H}_d$ ), 2.64–2.58 (m, 8H,  $\text{H}_{g+i+n+p}$ ), 2.45–2.40 (m, 2H,  $\text{H}_b$ ), 2.04–1.97 (m, 3H,  $\text{H}_{a+c}$ ), 1.96–1.89 (m, 4H,

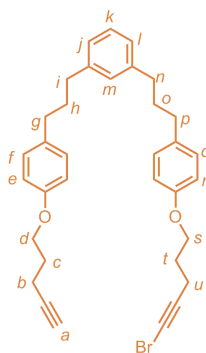


$H_{\text{H+O}}$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 156.9, 153.4, 142.2 (x 2), 134.5, 134.4, 129.4, 129.2, 128.6, 128.1, 125.7 (x 2), 115.0, 114.3, 83.5, 68.7, 66.1, 35.3 (x 2), 34.5 (x 2), 33.1 (x 2), 28.2, 15.1. LRESI-MS:  $m/z$  = 411  $[\text{M}-\text{H}]^-$ . HRESI-MS:  $m/z$  = 411.2319  $[\text{M}-\text{H}]^-$  (calcd. for  $\text{C}_{29}\text{H}_{31}\text{O}_2$ , 411.2330  $[\text{M}-\text{H}]^-$ ).



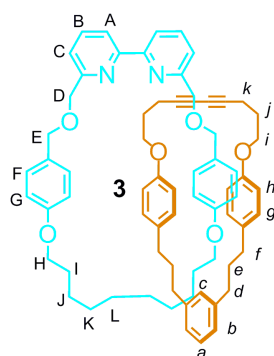
**18**

To a suspension of the alkyne **16** (0.48 g, 2.0 mmol, 1 eq.) and N-bromosuccinimide (0.39 g, 2.2 mmol, 1.1 eq.) in acetone (8 mL) was added  $\text{AgNO}_3$  (34 mg, 0.20 mmol, 0.1 eq.), and the reaction stirred at RT for 2 h. The mixture was then diluted with petroleum ether (b.p. 40-60 °C) and washed with water (50 mL). The aqueous layer was separated and extracted with diethyl ether (3 × 50 mL) and the combined organic fractions were then dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The resulting crude oil was purified by column chromatography on silica (petroleum ether:ethyl acetate 15:1) to yield **18** as a yellow oil (0.60 g, yield = 95%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.78 (d,  $J$  = 8.0, 2H,  $H_c$ ), 7.35 (d,  $J$  = 8.0, 2H,  $H_b$ ), 4.10 (t,  $J$  = 8.0, 2H,  $H_d$ ), 2.44 (s, 3H,  $H_a$ ), 2.26 (t,  $J$  = 8.0, 2H,  $H_f$ ), 1.85-1.79 (m, 2H,  $H_e$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 144.9, 132.7, 130.0, 127.9, 78.0, 68.6, 39.3, 27.5, 21.7, 15.9. LRESI-MS:  $m/z$  = 317  $[\text{M}^{79}\text{Br}+\text{H}]^+$ , 319  $[\text{M}^{81}\text{Br}+\text{H}]^+$ . HRESI-MS:  $m/z$  = 316.9844  $[\text{M}^{79}\text{Br}+\text{H}]^+$  (calcd. for  $\text{C}_{12}\text{H}_{14}^{79}\text{BrO}_3\text{S}$ , 316.9847  $[\text{M}^{79}\text{Br}+\text{H}]^+$ ).

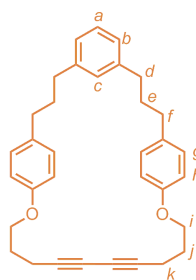


## 2

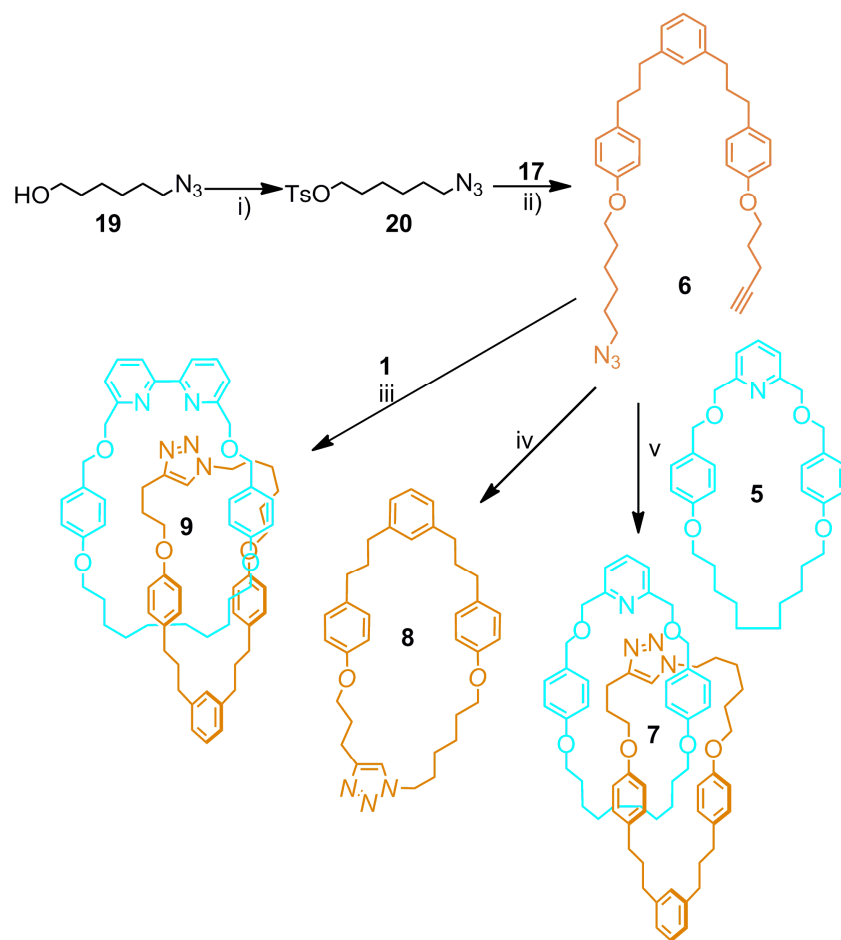
To a solution of **17** (0.30 g, 0.73 mmol, 1.0 eq.) and **18** (0.28 g, 0.88 mmol, 1.2 eq.) in DMF (20 mL) was added  $\text{Cs}_2\text{CO}_3$  (0.94 g, 2.9 mmol, 4.0 eq.) and the resulting suspension heated at 100 °C for 18 h. After cooling, the reaction was poured into ethyl acetate (50 mL) and then quenched with 1 M HCl (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 50 mL) and the combined organic extracts were washed with brine (50 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The resulting crude oil was purified by column chromatography on silica (petroleum ether: $\text{CH}_2\text{Cl}_2$  5:1) to yield **2** as a colorless oil (0.38 g, yield = 93%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.19 (t,  $J$  = 7.6, 1H,  $\text{H}_k$ ), 7.09-7.07 (m, 4H,  $\text{H}_{f+q}$ ), 7.01-6.99 (m, 3H,  $\text{H}_{j+l+m}$ ), 6.83-6.81 (m, 4H,  $\text{H}_{e+r}$ ), 4.06-4.01 (m, 4H,  $\text{H}_{d+s}$ ), 2.62-2.57 (m, 8H,  $\text{H}_{g+i+n+p}$ ), 2.44-2.38 (m, 4H,  $\text{H}_{b+u}$ ), 2.02-1.87 (m, 9H,  $\text{H}_{a+c+h+o+t}$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 157.0, 156.9, 142.3 (x 2), 134.5 (x 2), 129.3 (x 2), 128.6, 128.2, 125.8 (x 2), 114.3 (x 2), 83.6, 79.4, 68.8, 66.1 (x 2), 38.4, 35.3 (x 2), 34.5 (x 2), 33.2 (x 2), 28.2, 28.1, 16.5, 15.2. LRESI-MS:  $m/z$  = 556  $[\text{M}^{79}\text{Br}]^+$ , 558  $[\text{M}^{81}\text{Br}]^+$ . HRESI-MS:  $m/z$  = 556.1979  $[\text{M}^{79}\text{Br}]^+$  (calcd. for  $\text{C}_{34}\text{H}_{37}^{79}\text{BrO}_2$ , 556.1977  $[\text{M}^{79}\text{Br}]^+$ ).



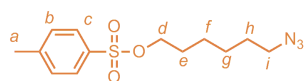
To a solution of **2** (56 mg, 0.10 mmol 5 eq.) in THF (0.2 mL) at  $-78\text{ }^{\circ}\text{C}$  was added LiHMDS (1.0 M in THF, 0.10 mL, 0.10 mmol, 5 eq.) and the mixture was stirred for 30 minutes at  $-78\text{ }^{\circ}\text{C}$ , after which time the reaction mixture was transferred to a flask containing CuI (4.0 mg, 20  $\mu\text{mol}$ , 1 eq.) and macrocycle **1** (11 mg, 20  $\mu\text{mol}$ , 1 eq.) in THF (0.3 mL). The reaction mixture was then allowed to stir for a further 72 h at RT. After this time, the reaction was cooled to  $0\text{ }^{\circ}\text{C}$  and quenched by addition of 17.5%  $\text{NH}_3(\text{aq})$  saturated with EDTA (1 mL) and allowed to stir in air for 40 minutes, during which time the aqueous layer turned blue. The organic layer was separated, washed with brine and dried over  $\text{MgSO}_4$ . After removal of the solvents in vacuo, the resulting crude oil was purified by column chromatography on silica ( $\text{CH}_2\text{Cl}_2$ :acetonitrile 10:1) to yield **3** as a colorless oil (4.3 mg, yield = 21%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.07 (d,  $J$  = 7.7, 2H,  $\text{H}_\text{A}$ ), 7.64 (t,  $J$  = 7.7, 2H,  $\text{H}_\text{B}$ ), 7.35 (d,  $J$  = 7.7, 2H,  $\text{H}_\text{C}$ ), 7.14-7.09 (m, 5H,  $\text{H}_{\text{a+f}}$ ), 6.93-6.89 (m, 2H,  $\text{H}_\text{b}$ ), 6.76 (d,  $J$  = 8.5, 4H,  $\text{H}_\text{g}$ ), 6.70 (s, 1H,  $\text{H}_\text{c}$ ), 6.66 (d,  $J$  = 8.6, 4H,  $\text{H}_\text{G}$ ), 6.48 (d,  $J$  = 8.5, 4H,  $\text{H}_\text{h}$ ), 4.60-4.58 (m, 8H,  $\text{H}_{\text{D+E}}$ ), 3.75-3.67 (m, 8H,  $\text{H}_{\text{i+H}}$ ), 2.40-2.34 (m, 8H,  $\text{H}_{\text{d+f}}$ ), 2.30 (t,  $J$  = 6.1, 4H,  $\text{H}_\text{k}$ ), 1.71-1.61 (m, 8H,  $\text{H}_{\text{e+j}}$ ), 1.49-1.42 (m, 4H,  $\text{H}_\text{l}$ ), 1.43-1.10 (m, 12H,  $\text{H}_{\text{J+K+L}}$ );  $^{13}\text{C}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 158.4, 158.1, 156.3, 155.1, 142.3, 136.7, 133.9, 129.5, 129.0, 127.8, 127.4, 125.5, 121.0, 119.4, 114.1 (x 2), 113.7, 76.0, 72.2, 67.4, 65.7, 64.6, 62.6, 34.9, 34.8, 34.6, 28.6, 28.5, 27.3, 25.4, 18.6, 15.1. LRESI-MS:  $m/z$  = 1044  $[\text{M}+\text{H}]^+$ . HRFAB-MS:  $m/z$  = 1043.5951  $[\text{M}+\text{H}]^+$  (calcd. for  $\text{C}_{70}\text{H}_{79}\text{O}_6\text{N}_2$ , 1043.5938  $[\text{M}+\text{H}]^+$ ).

**4**

To a solution of **2** (22 mg, 40  $\mu$ mol, 1 eq.) in THF (0.2 mL) at  $-78\text{ }^{\circ}\text{C}$  was added LiHMDS (1.0 M in THF, 40  $\mu$ L, 40  $\mu$ mol, 1 eq.) and the mixture was stirred for 30 minutes at  $-78\text{ }^{\circ}\text{C}$ , after which time the reaction mixture was transferred to a flask containing CuI (7.6 mg, 40  $\mu$ mol, 1 eq.) in THF (0.6 mL). The reaction mixture was allowed to stir for a further 7 days at RT. After this time, the reaction mixture was cooled to  $0\text{ }^{\circ}\text{C}$  and quenched by addition of 17.5%  $\text{NH}_3(\text{aq})$  saturated with EDTA (1 mL) and allowed to stir in air for 40 minutes, during which time the aqueous layer turned blue. The organic layer was separated, washed with brine and dried over  $\text{MgSO}_4$ . After removal of the solvents under reduced pressure, the resulting crude oil was purified by column chromatography on silica (petroleum ether:ethyl acetate 50:1) to yield **4** as a colorless oil (2.2 mg, yield = 12%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.18 (t,  $J$  = 7.6, 1H,  $\text{H}_a$ ), 7.08 (d,  $J$  = 8.4, 4H,  $\text{H}_g$ ), 7.01-6.99 (m, 3H,  $\text{H}_{b+c}$ ), 6.80 (d,  $J$  = 8.4, 4H,  $\text{H}_h$ ), 4.01-3.98 (m, 4H,  $\text{H}_i$ ), 2.62-2.56 (m, 8H,  $\text{H}_{d+f}$ ), 2.48-2.44 (m, 4H,  $\text{H}_k$ ), 2.00-1.86 (m, 8H,  $\text{H}_{j+e}$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 156.8, 142.2, 134.5, 129.2, 128.6, 128.1, 125.7, 114.3, 76.6, 66.0, 65.7, 35.3, 34.5, 33.2, 28.1, 16.0. LRESI-MS:  $m/z$  = 477  $[\text{M}+\text{H}]^+$ . HRESI-MS; 477.2792  $[\text{M}+\text{H}]^+$  (calcd. for  $\text{C}_{34}\text{H}_{37}\text{O}_2$ , 477.2794  $[\text{M}+\text{H}]^+$ ).



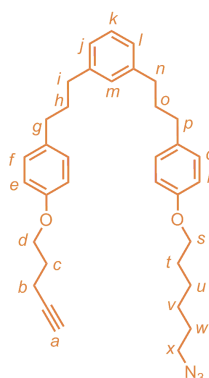
**Scheme 3.6.** (i)  $\text{Et}_3\text{N}$ ,  $p\text{-TsCl}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0\text{ }^\circ\text{C} \rightarrow \text{RT}$ , 18 h, 86%; (ii)  $\text{K}_2\text{CO}_3$ , DMF,  $80\text{ }^\circ\text{C}$ , 18 h, 34%; (iii)  $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$ , 1,2-dichloroethane,  $80\text{ }^\circ\text{C}$ , 170 h, 49%; (iv)  $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$ , 1,2-dichloroethane,  $80\text{ }^\circ\text{C}$ , 18 h, 41%; (v)  $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$ , 1,2-dichloroethane,  $80\text{ }^\circ\text{C}$ , 12 d, 53%.



**20**

To a solution of **19**<sup>19</sup> (1.80 g, 12.6 mmol, 1 eq.) and  $\text{Et}_3\text{N}$  (1.53 g, 2.10 mL, 15.1 mmol, 1.2 eq.) in  $\text{CH}_2\text{Cl}_2$  (100 mL) at  $0\text{ }^\circ\text{C}$  was added  $p\text{-toluenesulfonyl chloride}$  (2.88 g, 15.1 mmol, 1.2 eq.) and the reaction allowed to stir at RT for 18 h. After this time, the reaction was filtered through a pad of celite, and the celite washed with ethyl acetate (50 mL). The combined filtrates were then washed with water (50 mL) and

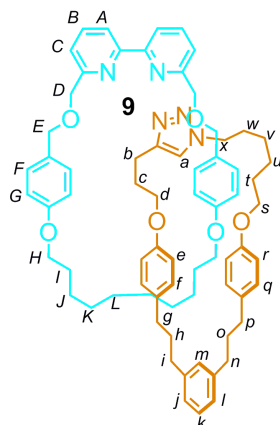
the aqueous phase extracted with ethyl acetate (3 × 50 mL). The combined organic fractions were washed with brine (50 mL) and dried (MgSO<sub>4</sub>). After filtration and concentration under reduced pressure, the resulting crude oil was purified by column chromatography on silica (hexane:ethyl acetate 15:1) to yield **20** as a colorless oil (3.21 g, yield = 86%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.78 (d, *J* = 8.0, 2H, H<sub>c</sub>), 7.35 (d, *J* = 8.0, 2H, H<sub>b</sub>), 4.10 (t, *J* = 6.4, 2H, H<sub>d</sub>), 3.22 (t, *J* = 6.8, 2H, H<sub>i</sub>) 2.45 (s, 3H, H<sub>a</sub>), 1.68-1.61 (m, 2H, H<sub>e</sub>), 1.57-1.51 (m, 2H, H<sub>h</sub>), 1.34-1.31 (m, 4H, H<sub>f+g</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 144.7, 133.1, 129.8, 127.9, 70.3, 51.2, 28.7, 28.6, 26.1, 25.0, 21.6. LRESI-MS: *m/z* = 298 [M+H]<sup>+</sup>. HRESI-MS: *m/z* = 298.1226 [M+H]<sup>+</sup>. (calcd. for C<sub>13</sub>H<sub>20</sub>N<sub>3</sub>O<sub>3</sub>S, 298.1225 [M+H]<sup>+</sup>).



## 6

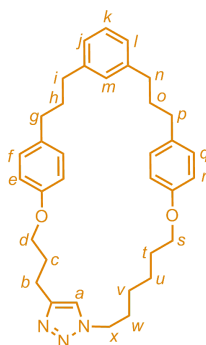
To a solution of **17** (0.21 g, 0.50 mmol, 1 eq.) and **20** (0.22 g, 0.75 mmol, 1.5 eq.) in DMF (1.5 mL) was added K<sub>2</sub>CO<sub>3</sub> (0.21 g, 1.5 mmol, 3.0 eq.) and the suspension heated to 80 °C for 18 h. After cooling to RT, the reaction mixture was poured into ethyl acetate (50 mL) and quenched with 1 M HCl (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 50 mL), and the combined organic fractions were washed with brine (50 mL), dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The resulting crude oil was then purified by column chromatography on silica (petroleum ether: ethyl acetate 20:1) to yield **6** as a colorless oil (90 mg, yield = 34%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.17 (t, *J* = 7.6, 1H, H<sub>k</sub>), 7.10-7.06 (m, 4H, H<sub>f+q</sub>), 7.00-6.99 (m, 3H, H<sub>i+l+m</sub>), 6.84-6.80 (m, 4H, H<sub>e+r</sub>), 4.04 (t, *J* = 6.0, 2H, H<sub>d</sub>), 3.93 (t, *J* = 6.4, 2H, H<sub>s</sub>), 3.28 (t, *J* = 6.8, 2H, H<sub>x</sub>), 2.62-2.56 (m, 8H,

$H_{g+i+n+p}$ ), 2.43-2.38 (m, 2H,  $H_b$ ), 2.02-1.87 (m, 7H,  $H_{a+c+h+o}$ ), 1.82-1.75 (m, 2H,  $H_t$ ), 1.69-1.39 (m, 6H,  $H_{u+v+w}$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 157.1, 156.9, 142.3, 142.2, 134.4, 134.3, 129.2 (x 2), 128.5, 128.1, 125.7 (x 2), 114.3, 114.2, 83.5, 68.7, 67.6, 66.0, 51.3, 35.3 (x 2), 34.5 (x 2), 33.2 (x 2), 29.1, 28.7, 28.2, 26.4, 25.6, 15.1. LRESI-MS:  $m/z$  = 538  $[\text{M}+\text{H}]^+$ . HRESI-MS:  $m/z$  = 537.3346  $[\text{M}]^+$  (calcd. for  $\text{C}_{35}\text{H}_{43}\text{N}_3\text{O}_2$ , 537.3355  $[\text{M}]^+$ ).



To a solution of macrocycle **1** (24 mg, 42  $\mu\text{mol}$ , 1 eq.) and  $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$  (16 mg, 42  $\mu\text{mol}$ , 1 eq.) in 1,2-dichloroethane (9 mL) was added compound **6** (95 mg, 0.18 mmol, 4 eq.) and the reaction mixture heated at 80 °C for 170 h. After this time, the reaction mixture was allowed to cool to RT and 17.5%  $\text{NH}_3(\text{aq})$  saturated with EDTA (9 mL) was added and the resulting mixture stirred vigorously for 10 minutes. The phases were separated and the organic phase was diluted with  $\text{CH}_2\text{Cl}_2$  (20 mL) then washed with 17.5%  $\text{NH}_3(\text{aq})$  saturated with EDTA (30 mL), water (3 x 30 mL) and brine (30 mL), dried ( $\text{MgSO}_4$ ) and evaporated under reduced pressure. The resulting residue was purified by flash chromatography on silica (1.  $\text{CH}_2\text{Cl}_2$ , 2.  $\text{CH}_2\text{Cl}_2$  with 5 $\rightarrow$ 20%  $\text{CH}_3\text{CN}$ ) to give catenane **9** as a colorless film (23 mg, 49%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.97 (d,  $J$  = 7.6, 2H,  $H_A$ ), 7.59 (t,  $J$  = 7.6, 2H,  $H_B$ ), 7.30 (d,  $J$  = 7.6, 2H,  $H_C$ ), 7.11 (t,  $J$  = 7.8, 1H,  $H_K$ ), 6.95-6.81 (m, 11H,  $H_{a+f+j+l+q+f}$ ), 6.66 (d,  $J$  = 8.6, 2H,  $H_{(e \text{ or } r)}$ ), 6.61 (d,  $J$  = 8.6, 2H,  $H_{(e \text{ or } r)}$ ), 6.49-6.44 (m, 5H,  $H_{m+G}$ ), 4.50 (s, 4H,  $H_D$ ), 4.44 (d,  $J$  = 1.5, 4H,  $H_E$ ), 3.72-3.64 (m, 10H,  $H_{d+s+x+H}$ ), 2.79-2.75 (m, 2H,  $H_b$ ), 2.53-2.48 (m, 2H,  $H_{(g \text{ or } p)}$ ), 2.42-2.31 (m, 6H,  $H_{(g \text{ or } p)+i+n}$ ), 1.99-1.97 (m, 2H,  $H_C$ ), 1.71-1.63 (m, 2H,  $H_{(h \text{ or } o)}$ ), 1.59-

1.49 (m, 6H,  $H_{(h \text{ or } o)+l}$ ), 1.42-1.15 (m, 16H,  $H_{t+w+j+k+l}$ ), 1.13-1.02 (m, 4H,  $H_{u+v}$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 158.4, 158.2, 156.9, 156.7, 155.4, 146.0, 142.4, 142.3, 142.2, 136.9, 134.1, 134.0, 129.5, 129.3, 129.2 (x 2), 128.0, 127.6, 125.7 (x 2), 121.2, 119.7, 114.2, 114.1, 113.9, 72.1, 71.9, 67.5, 66.5, 65.1, 49.5, 35.5, 35.3, 35.1, 35.0, 34.5, 33.7, 33.4, 33.2, 30.1, 29.3, 28.8, 28.7, 28.1 (x 2), 25.7, 21.2. LRESI-MS:  $m/z$  = 1105  $[\text{M}]^+$  HRESI-MS:  $m/z$  = 1104.6571  $[\text{M}]^+$  (calcd. for  $\text{C}_{71}\text{H}_{86}\text{N}_5\text{O}_6$ , 1104.6578  $[\text{M}]^+$ ).

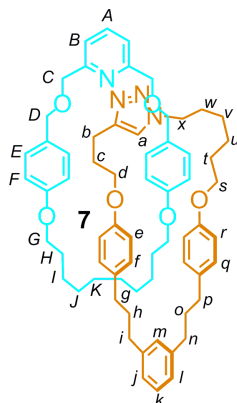


### 8

A solution of **6** (0.54 g, 1.0 mmol, 1 eq.) and  $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$  (0.37 g, 1.0 mmol, 1 eq.) in 1,2-dichloroethane (15 mL) was stirred at 80 °C for 18 h. After this time, the reaction mixture was allowed to cool to RT and 17.5%  $\text{NH}_3(\text{aq})$  saturated with EDTA (15 mL) was added and the resulting mixture stirred vigorously for 1 h. The phases were separated and the organic phase diluted with  $\text{CH}_2\text{Cl}_2$  (20 mL) then washed with 17.5%  $\text{NH}_3(\text{aq})$  saturated with EDTA (30 mL), water (3 x 30 mL) and brine (30 mL), dried ( $\text{MgSO}_4$ ) and evaporated under reduced pressure. The resulting crude oil was purified by column chromatography on silica ( $\text{CH}_2\text{Cl}_2$ :acetonitrile 30:1) to yield **8** as a colorless oil (0.22 g, yield = 41%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.24 (s, 1H,  $H_a$ ), 7.20 (t,  $J$  = 7.6, 1H,  $H_k$ ), 7.06-7.01 (m, 6H,  $H_{f+j+l+q}$ ), 6.86 (s, 1H,  $H_m$ ), 6.78-6.75 (m, 4H,  $H_{e+r}$ ), 4.29 (t,  $J$  = 7.2, 2H,  $H_x$ ), 3.94-3.88 (m, 4H,  $H_{d+s}$ ), 2.92 (t,  $J$  = 6.7, 2H,  $H_b$ ), 2.62-2.53 (m, 8H,  $H_{g+i+n+p}$ ), 2.18-2.10 (m, 2H,  $H_c$ ), 1.92-1.83 (m, 6H,  $H_{h+o+w}$ ), 1.77-1.70 (m, 2H,  $H_t$ ), 1.52-1.44 (m, 2H,  $H_u$ ), 1.38-1.31 (m, 2H,  $H_v$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 156.9 (x 2), 146.7, 142.2, 142.1, 134.3, 134.2, 129.3, 129.2, 128.1 (x 2), 125.9, 125.8, 121.2, 114.3, 114.2, 67.2, 65.8, 49.9, 35.3, 34.9, 34.5, 34.3, 33.2, 33.1, 30.1, 28.5, 28.3, 25.7,

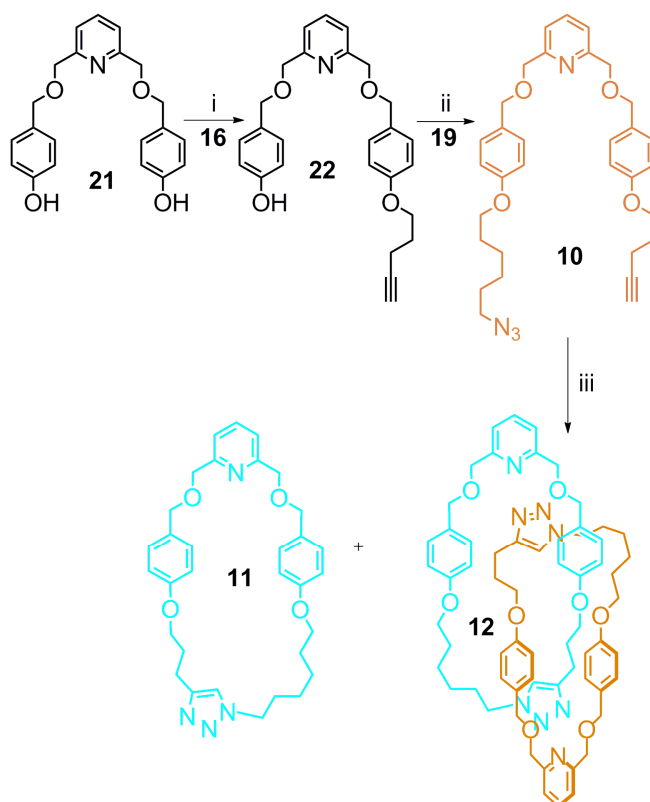


25.3, 21.5. LRESI-MS:  $m/z = 538 [M+H]^+$ . HRESI-MS:  $m/z = 538.3421 [M+H]^+$  (calcd. for  $C_{35}H_{44}N_3O_2$ , 538.3434  $[M+H]^+$ ).

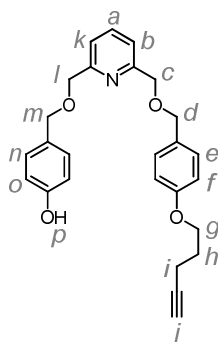


A solution of macrocycle **5**<sup>17</sup> (16 mg, 33  $\mu$ mol, 1 eq.), compound **6** (86 mg, 160  $\mu$ mol, 5 eq.) and  $[Cu(MeCN)_4]PF_6$  (12 mg, 33  $\mu$ mol, 1 eq.) in degassed 1,2-dichloroethane (26 mL) was heated at 80 °C for 12 days. The reaction mixture was then allowed to cool to RT before being washed with a saturated aqueous solution of EDTA/ $K_2CO_3$  (20 mL). The layers were then separated and the aqueous fraction extracted with  $CH_2Cl_2$  (2 x 20 mL). The combined organic extracts were then washed with brine (20 mL), dried ( $Na_2SO_4$ ) and concentrated under reduced pressure to give a yellow residue, which was purified by flash column chromatography on silica (10%  $CH_3CN$  in  $CH_2Cl_2$ , followed by 10%  $CH_3CN$  in  $CH_2Cl_2$  with 2% methanol) to give **7** as a pale yellow oil (18 mg, 53%).  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  = 7.55 (t,  $J$  = 7.7, 1H,  $H_A$ ), 7.22 (d,  $J$  = 7.7, 2H,  $H_B$ ), 7.13 (t,  $J$  = 7.5, 1H,  $H_K$ ), 7.00-6.86 (m, 11H,  $H_{a+f+j+l+q+E}$ ), 6.70-6.65 (m, 4H,  $H_{e+r}$ ), 6.54-6.51 (m, 5H,  $H_{m+f}$ ), 4.42-4.34 (m, 4H,  $H_C$ ), 4.17 (s, 4H,  $H_D$ ), 3.78-3.73 (m, 6H,  $H_{d+g}$ ), 3.68 (t,  $J$  = 5.7, 2H,  $H_S$ ), 3.59-3.55 (m, 2H,  $H_X$ ), 2.79 (t,  $J$  = 7.5, 2H,  $H_b$ ), 2.57-2.53 (m, 2H,  $H_{(g \text{ or } p)}$ ), 2.45-2.36 (m, 6H,  $H_{(g \text{ or } p)+i+n}$ ), 2.04-1.98 (m, 2H,  $H_C$ ), 1.76-1.70 (m, 2H,  $H_{(h \text{ or } o)}$ ), 1.63-1.56 (m, 6H,  $H_{(h \text{ or } o)+H}$ ), 1.43-1.36 (m, 2H,  $H_t$ ), 1.32-1.19 (m, 6H,  $H_{w+i}$ ), 1.15-0.98 (m, 10H,  $H_{u+j+k}$ ), 0.81-0.71 (m, 2H,  $H_v$ );  $^{13}C$  NMR (100 MHz,  $CDCl_3$ ):  $\delta$  = 158.6, 157.5, 156.9, 156.7, 145.9, 142.4, 142.3, 136.8, 134.1, 134.0, 129.9, 129.3, 129.1, 129.0, 128.0, 127.6, 125.7, 125.5, 121.4, 119.3, 114.3, 114.1, 114.0, 72.2, 70.6,

66.9, 66.6, 65.2, 49.4, 35.5, 35.0 (x 2), 33.8, 33.4, 29.9, 29.6, 28.7, 28.5 (x 2), 28.1 (x 2), 25.6, 25.3, 24.9, 21.2. LRESI-MS:  $m/z = 1028 [M+H]^+$  HRESI-MS:  $m/z = 1027.6336 [M+H]^+$  (calcd. for  $C_{66}H_{83}N_4O_6$ , 1027.6313  $[M+H]^+$ ).

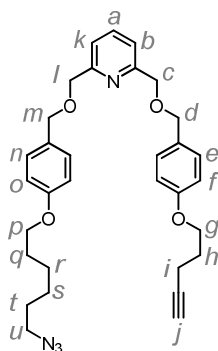


**Scheme 3.7.** i)  $CS_2CO_3$ , DMF, 55 °C, 3 h, 40%; ii)  $CS_2CO_3$ , DMF, 55 °C, 18 h, 96%; iii)  $[Cu(MeCN)_4]PF_6$ , 1,2-dichloroethane, 80 °C, 120 h, 46% (**12**) and 6% (**11**).

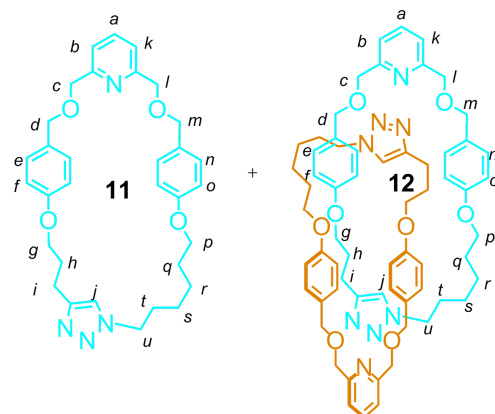


## 22

**16** (678 mg, 2.85 mmol, 1 eq.) was added to a solution of diphenol **21** (1.00 g, 2.85 mmol, 1 eq.) and  $\text{Cs}_2\text{CO}_3$  (1.39 g, 4.27 mmol, 1.5 eq.) in DMF (25 mL) and the reaction mixture heated at 55 °C for 3 h. The reaction mixture was then allowed to cool to RT and ethyl acetate (200 mL) and water (200 mL) were added. The phases were separated and the organic phase washed with water (3 x 200 mL) and brine (200 mL), dried ( $\text{MgSO}_4$ ) and evaporated under reduced pressure. The resulting residue was purified by flash chromatography on silica (1.  $\text{CH}_2\text{Cl}_2$ , 2.  $\text{CH}_2\text{Cl}_2$  with 10→20% ethyl acetate) to give alkyne **22** (474 mg, 40%) as a yellow oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.75 (t,  $J$  = 7.7, 1H,  $\text{H}_a$ ), 7.43-7.41 (m, 2H,  $\text{H}_{b+k}$ ), 7.27 (d,  $J$  = 8.5, 2H,  $\text{H}_e$ ), 7.16 (d,  $J$  = 8.5, 2H,  $\text{H}_n$ ), 6.86 (d,  $J$  = 8.5, 2H,  $\text{H}_f$ ), 6.72 (d,  $J$  = 8.5, 2H,  $\text{H}_o$ ), 4.65 (s, 2H,  $\text{H}(\text{c or l})$ ), 4.62 (s, 2H,  $\text{H}(\text{c or l})$ ), 4.54 (m, 4H,  $\text{H}_{d+m}$ ), 4.06 (t,  $J$  = 6.1, 2H,  $\text{H}_g$ ), 2.40 (dt,  $J_1$  = 7.0,  $J_2$  = 2.6, 2H,  $\text{H}_i$ ), 2.07-1.97 (m, 3H,  $\text{H}_{h+j}$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 158.5, 157.7 (x 2), 155.9, 137.8, 129.9, 129.8, 129.5, 129.0, 120.3 (x 2), 115.2, 114.4, 83.4, 72.7, 72.6, 72.1, 71.7, 68.8, 66.0, 28.1, 15.1. LRESI-MS:  $m/z$  = 417  $[\text{M}]^+$ . HRESI-MS:  $m/z$  = 418.2021  $[\text{M}+\text{H}]^+$  (calc. for  $\text{C}_{26}\text{H}_{28}\text{O}_4\text{N}_1$ , 418.2013  $[\text{M}+\text{H}]^+$ ).

**10**

**17** (267 mg, 898  $\mu\text{mol}$ , 1.5 eq.) was added to a solution of phenol **22** (250 mg, 600  $\mu\text{mol}$ , 1 eq.) and  $\text{Cs}_2\text{CO}_3$  (586 mg, 1.80 mmol, 3 eq.) in DMF (6 mL) and the reaction mixture heated at 55  $^\circ\text{C}$  for 18 h. The reaction mixture was allowed to cool to RT and ethyl acetate (40 mL) and water (40 mL) were added. The phases were separated and the organic phase was washed with water (3 x 40 mL) and brine (40 mL), dried ( $\text{MgSO}_4$ ) and evaporated under reduced pressure. The resulting residue was purified by flash column chromatography on silica (1.  $\text{CH}_2\text{Cl}_2$ , 2. 9:1  $\text{CH}_2\text{Cl}_2$ :ethyl acetate) to give **10** (313 mg, 96%) as a yellow oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.71 (t,  $J$  = 7.7, 1H,  $\text{H}_a$ ), 7.39-7.37 (m, 2H,  $\text{H}_{b+k}$ ), 7.32-7.28 (m, 4H,  $\text{H}_{e+n}$ ), 6.91-6.85 (m, 4H,  $\text{H}_{f+o}$ ), 4.64 (s, 4H,  $\text{H}_{c+l}$ ), 4.57 (s, 4H,  $\text{H}_{d+m}$ ), 4.07 (t,  $J$  = 6.1, 2H,  $\text{H}_g$ ), 3.96 (t,  $J$  = 6.4, 2H,  $\text{H}_p$ ), 3.28 (t,  $J$  = 6.9, 2H,  $\text{H}_u$ ), 2.41 (dt,  $J_1$  = 7.0,  $J_2$  = 2.6, 2H,  $\text{H}_i$ ), 2.05-1.95 (m, 3H,  $\text{H}_{h+j}$ ), 1.83-1.75 (m, 2H,  $\text{H}_q$ ), 1.68-1.59 (m, 2H,  $\text{H}_t$ ), 1.55-1.38 (m, 4H,  $\text{H}_{r+s}$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 158.7, 158.5, 157.9 (x 2), 130.0, 129.8, 129.5 (x 2), 119.9, 114.4 (x 2), 114.3 (x 2), 83.4, 72.7 (x 2), 72.6 (x 2), 68.8, 67.6, 66.1, 51.3, 29.0, 28.7, 28.1, 26.4, 25.6, 15.1. LRESI-MS:  $m/z$  = 543  $[\text{M}+\text{H}]^+$ . HRESI-MS:  $m/z$  = 543.2955  $[\text{M}+\text{H}]^+$  (calc. for  $\text{C}_{32}\text{H}_{39}\text{O}_4\text{N}_4$ , 543.2971  $[\text{M}+\text{H}]^+$ ).



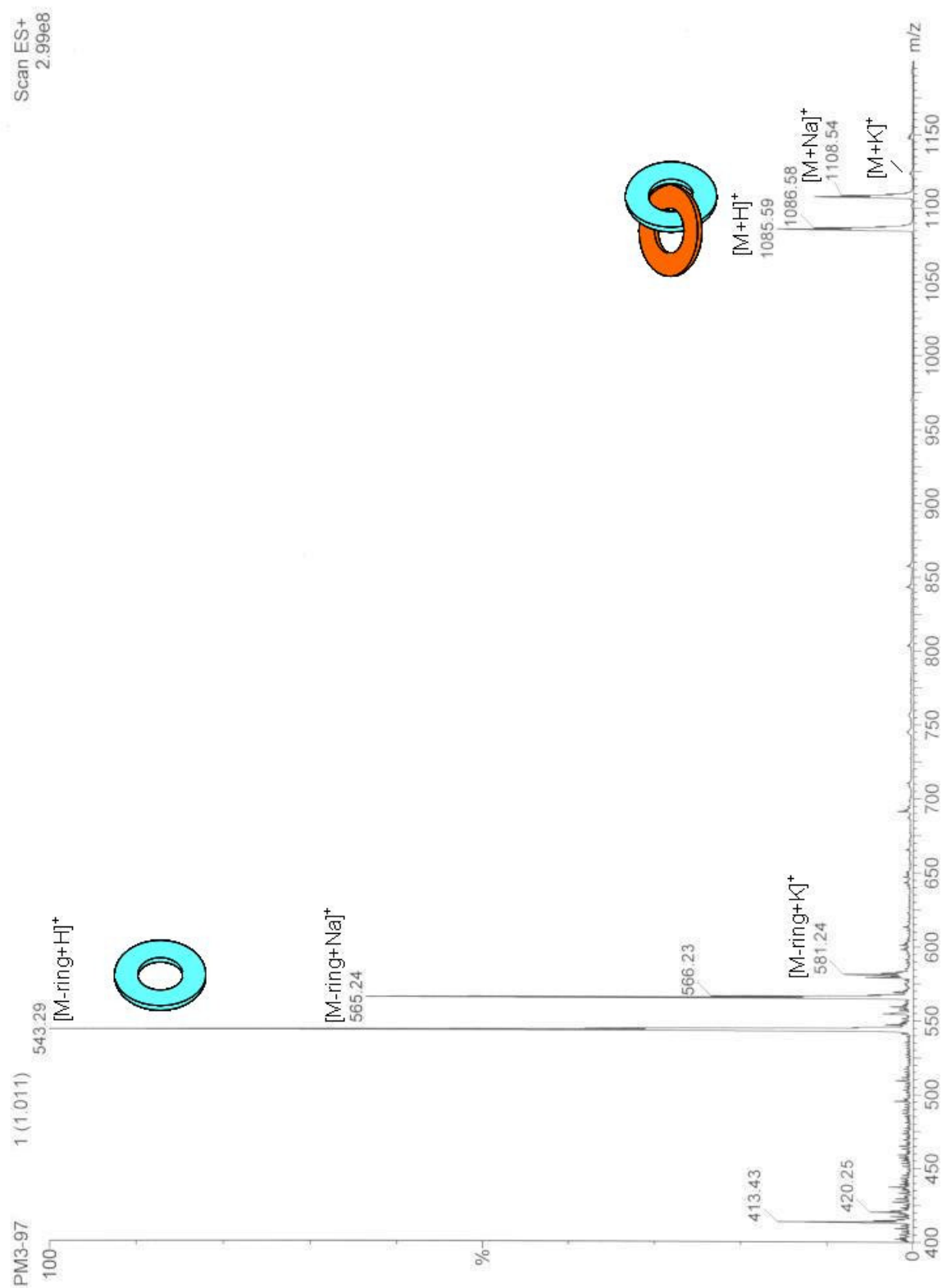
[Cu(MeCN)<sub>4</sub>]PF<sub>6</sub> (17 mg, 46 μmol, 0.5 eq.) was added to a solution of compound 10 (50 mg, 92 μmol, 1 eq.) in 1,2-dichloroethane (240 mL) and the reaction mixture heated at 80 °C for 120 h. After this time, the reaction mixture was allowed to cool to RT and 17.5% NH<sub>3</sub>(aq) saturated with EDTA (240 mL) was added and mixture stirred vigorously for 10 minutes. The phases were separated and the organic phase was washed with 17.5% NH<sub>3</sub>(aq) saturated with EDTA (240 mL), water (3 x 240 mL) and brine (240 mL), dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The resulting residue was purified by flash column chromatography on silica (1. ethyl acetate, 2. ethyl acetate with 2→5% acetone) to give catenane **12** (23 mg, 46%) as a yellow resin and macrocycle **11** (3 mg, 6%) as a colorless film.

**Catenane 12:** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.56 (t, *J* = 7.7, 2H, H<sub>a</sub>), 7.26-7.18 (m, 4H, H<sub>b+k</sub>), 7.13 (s, 2H, H<sub>j</sub>), 7.04 (d, *J* = 8.5, 4H, H<sub>(e or n)</sub>), 6.95 (d, *J* = 8.5, 4H, H<sub>(e or n)</sub>), 6.63-6.56 (m, 8H, H<sub>f+o</sub>), 4.45 (s, 4H, H<sub>(c or l)</sub>), 4.37 (s, 4H, H<sub>(c or l)</sub>), 4.22-4.19 (m, 8H, H<sub>d+m</sub>), 3.85-3.80 (m, 4H, H<sub>u</sub>), 3.75-3.71 (m, 8H, H<sub>g+p</sub>), 2.75 (t, *J* = 6.5, 4H, H<sub>i</sub>), 2.00-1.92 (m, 4H, H<sub>h</sub>), 1.55-1.45 (m, 8H, H<sub>q+t</sub>), 1.29-1.19 (m, 4H, H<sub>s</sub>), 1.08-0.98 (m, 4H, H<sub>r</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 158.6, 158.3, 157.5, 157.3, 146.0, 134.1, 129.9, 129.6, 129.4, 129.2, 121.8, 119.8, 119.6, 114.1, 114.0, 72.2 (x 2), 71.3, 70.7, 66.8, 65.5, 49.5, 30.0, 28.1 (x 2), 25.4, 25.0, 21.2. LRESI-MS: *m/z* = 1086 [M+H]<sup>+</sup>; HRFAB-MS (3-NOBA matrix): *m/z* = 1085.5853 [M+H]<sup>+</sup> (calc. for C<sub>64</sub>H<sub>77</sub>O<sub>8</sub>N<sub>8</sub>, 1085.5864 [M+H]<sup>+</sup>).

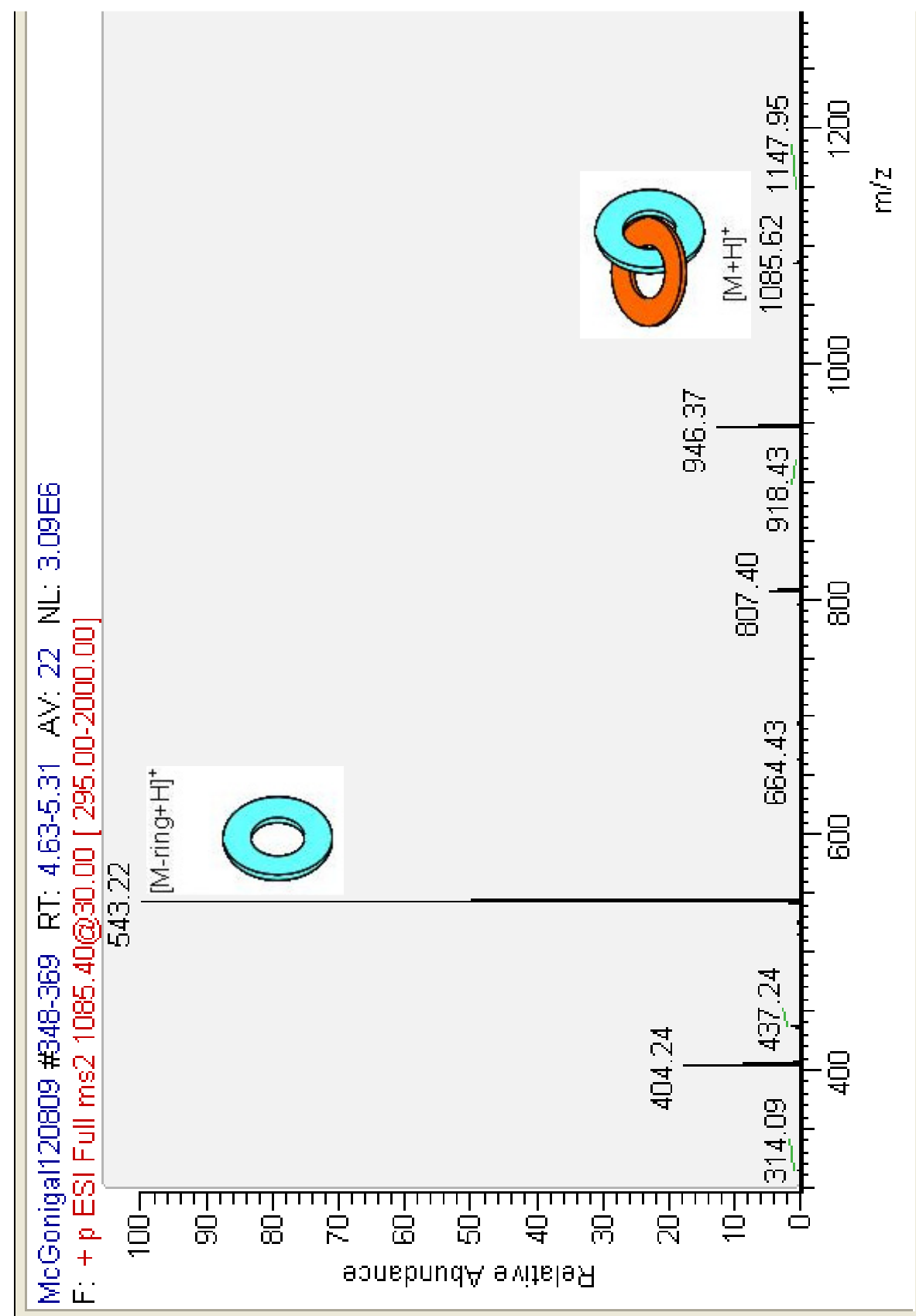
**Macrocycle 11:**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.69 (t,  $J$  = 7.7, 1H,  $\text{H}_a$ ), 7.38-7.34 (m, 2H,  $\text{H}_{b+k}$ ), 7.24-7.19 (m, 5H,  $\text{H}_{e+j+n}$ ), 6.78 (dd,  $J_1$  = 8.6,  $J_2$  = 1.7, 4H,  $\text{H}_{f+o}$ ), 4.60-4.58 (m, 4H,  $\text{H}_{c+l}$ ), 4.44-4.42 (m, 4H,  $\text{H}_{d+m}$ ), 4.30-4.25 (m, 2H,  $\text{H}_u$ ), 3.94 (t,  $J$  = 5.9, 2H,  $\text{H}_p$ ), 3.85 (t,  $J$  = 6.0, 2H,  $\text{H}_g$ ), 2.91 (t,  $J$  = 6.7, 2H,  $\text{H}_i$ ), 2.16-2.08 (m, 2H,  $\text{H}_h$ ), 1.92-1.82 (m, 2H,  $\text{H}_t$ ), 1.77-1.69 (m, 2H,  $\text{H}_q$ ), 1.52-1.43 (m, 2H,  $\text{H}_r$ ), 1.38-1.31 (m, 2H,  $\text{H}_s$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 158.6, 158.5, 157.9, 157.6, 146.4, 137.1, 130.0, 129.8, 129.6, 129.4, 121.3, 120.1, 119.9, 114.3, 114.1, 72.5, 72.4, 71.8, 71.1, 66.9, 65.4, 50.0, 30.4, 28.3, 28.2, 25.7, 25.2, 21.3. LRESI-MS:  $m/z$  = 543  $[\text{M}+\text{H}]^+$ ; HRESI-MS:  $m/z$  = 543.2984  $[\text{M}+\text{H}]^+$  (calc. for  $\text{C}_{32}\text{H}_{39}\text{O}_4\text{N}_4$ , 543.2971  $[\text{M}+\text{H}]^+$ ).

### 3.4.2. Fragmentation Data

#### LRMS Fragmentation Data



## MS-MS Fragmentation Data





### 3.5 References

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## Chapter 4

# Active Metal Template Synthesis of a Molecular Trefoil Knot

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## Synopsis

*Since the first discovery of topologically non-trivial structures in biochemistry – the naturally occurring molecular knots was reported in 1967, chemical topology has been a captivating subject for scientists. However, efficient template strategies for the design and synthesis of such knotted structures remain elusive. Taking this into account, the trefoil knot, the simplest prime knot, has attracted synthetic chemists' attention since the early days. In this chapter, an active metal-ion templated strategy for the preparation of a molecular trefoil knot is described. The key active metal template knotting reaction utilizes the combination of two bidentate ligand sites to create a cross-over point and the use of the Cu(I)-catalyzed azide alkyne cycloaddition (click) reaction to link the termini of the building block to form the trefoil knot. The topology of the product is inferred by comparison of the  $^1\text{H}$  NMR spectra and ion mobility mass spectrometry of the precursor, the simple macrocycle product, and the trefoil knot. Ion mobility MS studies provide a measure of the size and flexibility of the different species.*

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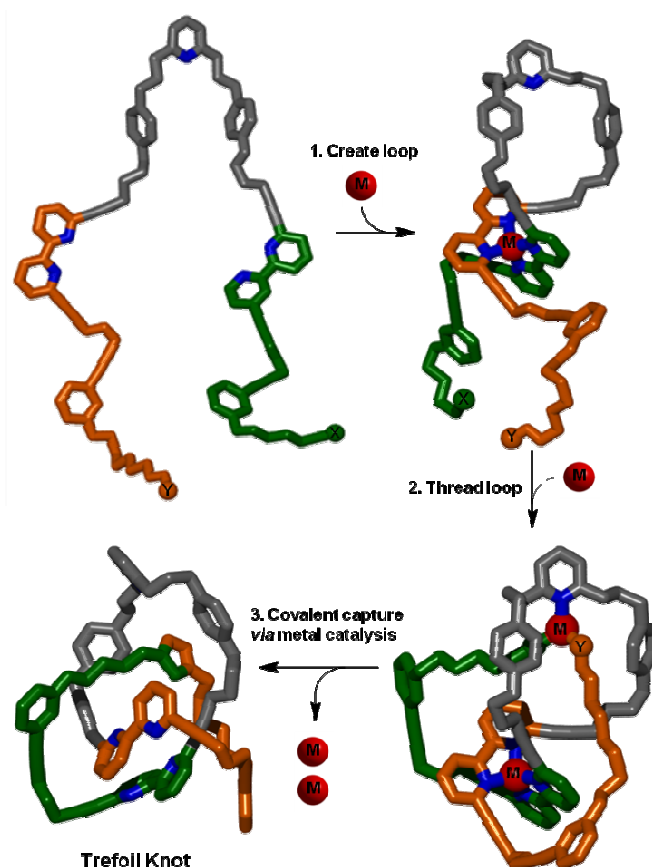
## 4.1 Introduction

Although many different approaches to catenanes and rotaxanes have been introduced in recent years,<sup>1</sup> few strategies have been successfully developed for the synthesis of molecular knots.<sup>2</sup> Trefoil knots, the simplest prime knot other than the topologically-trivial unknot (i.e. any ring or simple macrocycle), have been found in DNA,<sup>3</sup> proteins<sup>4</sup> and in synthetic polymers<sup>5</sup>. Sauvage and co-workers prepared the first synthetic molecular knot by using the preorganization of two ligand strands around two tetrahedral Cu<sup>I</sup> centers as the key template interaction to generate the three crossing points required for a trefoil knot.<sup>6</sup> Subsequently, donor–acceptor interactions,<sup>7</sup> Watson–Crick base pairing,<sup>8</sup> amide hydrogen bonding<sup>9</sup> and ligand folding about an octahedral metal ion<sup>10</sup> have all been used to template the formation of molecular trefoil knots.<sup>11</sup>

A few years ago a strategy for the synthesis of rotaxanes and catenanes was introduced in which metal ions play a dual role, acting as a template to entwine or thread the building blocks while also actively catalyzing the bond-forming reaction that covalently traps the interlocked structure.<sup>12</sup> This ‘active template’ approach has proven to be an effective route to various types of mechanically interlocked molecules and can be applied using an increasing number of different transition metal-catalyzed reactions.<sup>12j</sup> Here we report on an active template reaction that occurs through a loop generated through classical ‘passive template’ coordination to bring about the synthesis of the smallest trefoil knot prepared to date. The trefoil knot was characterized by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy, mass spectrometry and by drift tube ion mobility mass spectrometry (DT IM-MS) experiments that show that the molecular knot has a significantly smaller cross-sectional area (with a narrower distribution) than the corresponding open chain and unknot-macrocycle isomers.

## 4.2 Results and Discussion

To apply active template synthesis to a trefoil knot architecture we envisaged a system (Scheme 4.1) in which a single molecular strand with reactive functional groups at each terminus (X and Y) could be geometrically manipulated and knotted through multiple interactions with metal ions (M).



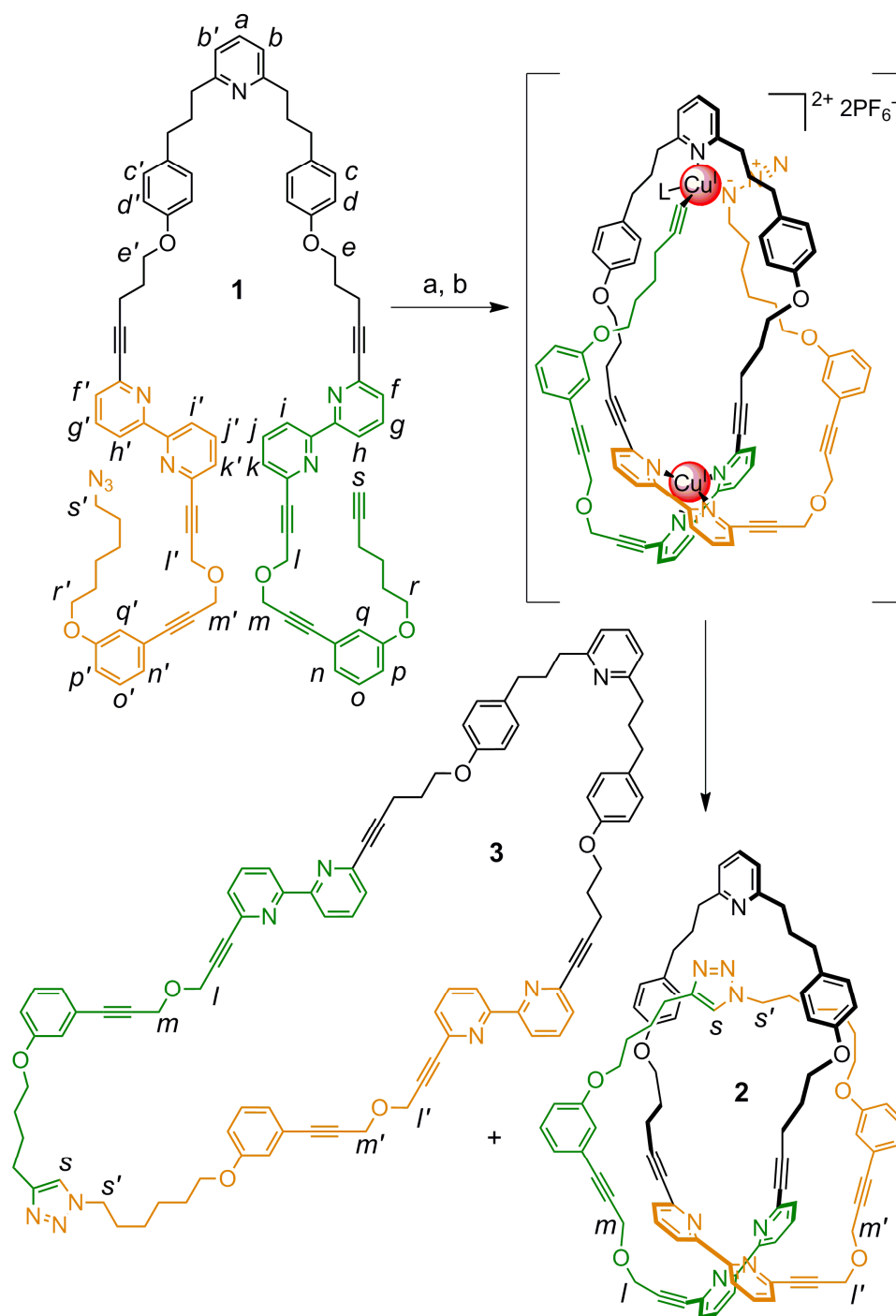
**Scheme 4.1.** Schematic representation of the active template synthesis of a molecular trefoil knot. A single-strand ligand with one monodentate and two bidentate binding sites (blue) and two functional end groups (X and Y) is knotted by the action of metal ions (red, M). Step 1: One metal ion creates a loop via coordination to the bidentate binding sites. Step 2: The other metal ion binds to the functional end groups and, through its preferred coordination geometry, threads the loop. Step 3: The knotted architecture is captured by metal-catalyzed covalent bond formation between X and Y.

First, a loop in the strand would be formed by coordination of two bidentate binding sites in the strand to a tetrahedral metal ion (Scheme 4.1, step 1). A second metal ion, bound endotopically within the loop by a monodentate ligating site, would then

perform the two-fold tasks of (i) gathering both functional end groups in an orientation, dictated by the metal's preferred coordination geometry, that places them on opposite sides of the loop (Scheme 4.1, step 2), and (ii) catalyzing a covalent bond forming reaction between the end groups to generate the molecular trefoil knot (Scheme 4.1, step 3).

Ligand **1** (Scheme 4.2) was synthesized in nine steps from commercially available starting materials (for experimental details see Supporting Information). The single-strand molecule has three potential metal binding sites: two bipyridyl groups to create the loop (and one of the three required crossing points) by chelation to a tetrahedral Cu<sup>I</sup> ion and a 2,6-pyridine unit to bind the catalytically-active metal center. The Cu<sup>I</sup>-catalyzed azide-alkyne cycloaddition<sup>13</sup> (CuAAC) 'click' reaction was chosen for the covalent-capture reaction that forms the remaining two crossing points as it utilizes Cu<sup>I</sup> (avoiding the complication of having different types of metal ions in the reaction) and because previous studies have shown it to be highly effective in rotaxane- and catenane-forming active template reactions.<sup>12a,d,i,k,n,14</sup> Molecular modeling<sup>15</sup> was used to estimate an appropriate length for the alkyl chain spacers between the functional end groups and the Cu<sup>I</sup> binding sites.

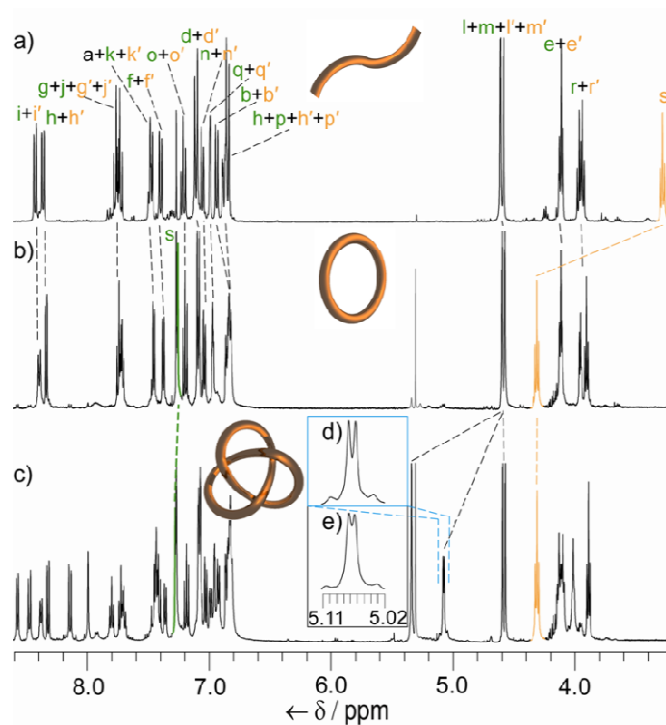
We initially investigated reaction conditions for the active metal template knotting reaction of ligand **1** (Scheme 4.2) using dichloromethane, chloroform and 1,2-dichloroethane, as these had proven effective in previous CuAAC active template reactions<sup>12a,d,i,k,n</sup>. However, upon addition of [Cu(CH<sub>3</sub>CN)<sub>4</sub>]PF<sub>6</sub> to a dilute solution of **1** in any of these halogenated solvents, a precipitate formed immediately.<sup>16</sup> After screening a number of solvent mixtures, 4:1 chloroform–nitromethane was found to retain the reactants and products in solution during the course of the reaction. An optimized concentration (1.5 mM) of **1**, with 1.5 molar equivalents<sup>17</sup> of [Cu(CH<sub>3</sub>CN)<sub>4</sub>]PF<sub>6</sub> at 60 °C, led to complete consumption of **1** after 4 days, as evidenced by <sup>1</sup>H NMR of the crude reaction mixture.



**Scheme 4.2.** Active metal template synthesis of trefoil knot **2**: a)  $\text{CHCl}_3\text{-CH}_3\text{NO}_2$  (4:1),  $[(\text{CH}_3\text{CN})_4\text{Cu}]\text{PF}_6$  (1.5 mole per 1 mole of **1**), 60 °C, 96 h; b)  $\text{Na}_2\text{EDTA}$ ,  $\text{NH}_3$ . **2** 24%, **3** 10%. Trefoil knots are topologically chiral;<sup>17</sup> only one enantiomer of **2** is shown.

#### 4.2.1 NMR Analysis of the Trefoil Knot

After demetallation through washing with a basic ethylenediaminetetraacetic acid disodium salt-ammonia ( $\text{Na}_2\text{EDTA-NH}_3$ ) solution,<sup>12g</sup> the reaction products were purified using a combination of size exclusion (SEC) and high performance liquid (HPLC) chromatographies. SEC enabled facile removal of the oligomeric byproducts and the resulting mixture was separated into its individual components by reverse phase preparative HPLC. Two products were isolated, in 24% and 10% yields, both of which were shown to be isomers of the acyclic starting material **1** by high resolution electrospray ionization-mass spectrometry (HRESI-MS) (see Figure 1 caption and the Supporting Information). The isomer formed in lower yield (10%) was identified as the simple macrocycle (i.e. a cyclic structure with unknot topology) **3** by comparison of its  $^1\text{H}$  NMR spectrum (Figure 4.1b) with that of the starting material **1** (Figure 1a). The spectrum of the flexible 75-membered-ring macrocycle (**3**) is very similar to that of the open chain isomer (**1**), the only significant differences being the shift of the  $\text{H}_{\text{S}}$  ( $-\text{NCH}_2-$ ) protons and  $\text{H}_{\text{S}}$  (from 2.0 ppm in **1** to 7.25 ppm in **3**) following conversion of the azide and terminal alkyne to the triazole ring.



**Figure 4.1.** Partial  $^1\text{H}$  NMR spectra (400 MHz,  $\text{CDCl}_3$ , 300 K) of three isomers (**1**, **2** and **3**) of molecular formula  $\text{C}_{88}\text{H}_{84}\text{N}_8\text{O}_6$ : building block (**1**) and the two products (**2** and **3**) isolated from the reaction of **1** shown in Scheme 2. The signals of the  $\text{H}_s$  protons, associated with the  $-\text{NCH}_2-$  group (adjacent to the azide in **1** and the triazole ring in **2** and **3**), are shown in orange. The signals of the  $\text{H}_s$  protons, associated with the  $-\text{CH}-$  of the triazole ring in **2** and **3**, are shown in green. a) Open chain building block **1**, HRESI-MS:  $m/z = 1361.6613$   $[\text{M}+\text{H}]^+$  (calc. for  $\text{C}_{88}\text{H}_{85}\text{N}_8\text{O}_6$  1361.6597). b) Unknot-macrocycle **3**, HRESI-MS:  $m/z = 1361.6603$   $[\text{M}+\text{H}]^+$ . c) Trefoil knot **2**, HRESI-MS:  $m/z = 1361.6601$   $[\text{M}+\text{H}]^+$ . d) 500 MHz and e) 400 MHz expansion of the region between 5.11 and 5.02 ppm of the spectrum of **2** showing a propargylic methylene ( $\text{H}_{l,l',m}$  or  $m'$ ) AB system ( $J_{\text{AB}} = 13.2$  Hz). The protons are diastereotopic as a consequence of the chirality of the trefoil knot. The lettering corresponds to that shown in Scheme 2.

The isomer isolated in greater yield (24%) was confirmed as the trefoil knot **2** through a series of NMR, mass spectrometry and DT IM-MS experiments. The  $^1\text{H}$  NMR spectrum of **2** (Figure 4.1c) is very different to those of its open chain **1** and unknot-macrocycle **3** isomers (Figure 4.1a and 1b). Many of the resonances in the aromatic region of **2** are separated into two sets of inequivalent signals. The increase in the overall number of resonances observed is a result of the loss of the

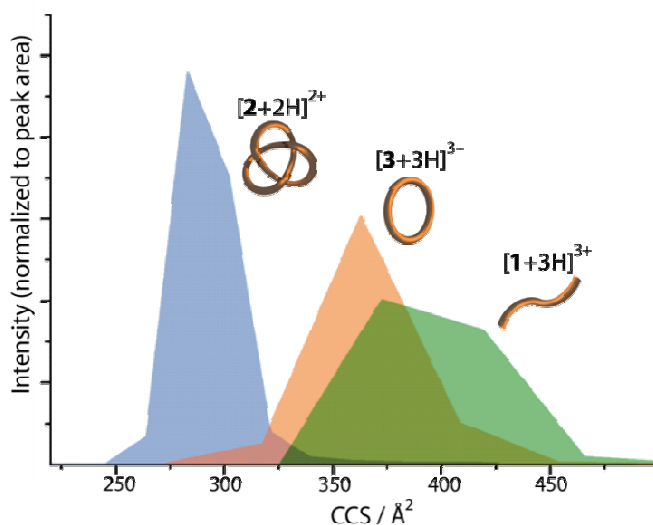
pseudosymmetry of **1** (and **3**) upon formation of the conformationally contorted trefoil knot structure—the 75 atom entwined loop is the smallest knot synthesized to date<sup>10c</sup>—and molecular modeling<sup>15</sup> and DT IM-MS results (vide infra) indicate it to be tightly wound. Two of the propargylic methylene resonances (two of H<sub>l/l'/m/m'</sub>) are shifted significantly downfield in **2** compared to the unknot-macrocyclic **3** (from 4.59 ppm to 5.33 and 5.07 ppm). It appears that these protons spend a significant amount of time face-on to an aromatic ring in low energy conformations of the knot and are shielded through ring current effects. Notably the propargylic methylene resonance at 5.07 ppm appears as an AB system (Figure 4.2d and 4.2e), indicating that the protons are diastereotopic.<sup>18</sup> This is a consequence of the inherent chirality of a trefoil knot.<sup>10d,19</sup>

#### 4.2.2 DT -IMMS Analysis of the Trefoil Knot

Further insight into the structure of trefoil knot **2** was provided by drift tube ion mobility mass spectrometry (DT IM-MS). In DT IM-MS experiments the velocity with which an ion travels through a cell containing a buffer gas (commonly helium), under the influence of a weak electric field, depends on the ion's collision cross section (CCS) with the buffer gas (averaged over all possible orientations of the ion).<sup>[20,21]</sup> A larger ion with few conformational restrictions takes longer to traverse the drift cell, undergoing more collisions with the buffer gas, than a smaller, more compact, structure. This has previously been demonstrated for naturally occurring antimicrobial peptides<sup>20</sup> and for synthetic cyclic and linear peptides<sup>21</sup>. With low charge numbers, flexible molecules may wrap tightly around the charged regions in order to solvate them with heteroatoms and aromatic rings. However, as the number of charges on a molecular ion increases, the size of the adopted conformations increases as electrostatic repulsions try to force the largest distance between the charges that the molecule will allow. In general, the more charge that a flexible structure carries, the larger the observed CCS. In addition to the magnitude of the CCS giving information about the size of the molecular ion, the broadness of the distribution indicates the flexibility (the number of differently sized and shaped conformations adopted) of the molecular structure.



Following nano-electrospray ionization, DT IM-MS showed significant differences in the rotationally-averaged CCS areas of ions of the three isomers **1-3** (Figure 2). The largest average CCS of the open chain isomer **1** ( $[1+3H]^{3+}$  ion) and unknot-macrocycle **3** ( $[3+3H]^{3+}$  ion) were  $395 (\pm 3.5) \text{ \AA}^2$  and  $368 (\pm 5.3) \text{ \AA}^2$ , respectively. The largest average CCS observed for the trefoil knot, **2**, ( $[2+2H]^{2+}$  ion) was  $292 (\pm 1) \text{ \AA}^2$ . So for the highest charge state observed for each species, open chain isomer **1** has a larger molecular cross section than unknot-macrocycle **3** which, in turn, has a much larger cross-sectional area than trefoil knot **2**. Furthermore, the open chain isomer **1** has the broadest CCS distribution, followed by the unknot-macrocycle **3**, with the trefoil knot **2** having the narrowest range. These results indicate that the trefoil knot has a much more compact and inflexible structure than the unknot-macrocycle, which is more compact and less flexible than the acyclic strand. Calculations of the expected CCS's from the Spartan-minimized<sup>15</sup> structures of the most extended form of each molecular species support the observed experimental trend (see Supporting Information).



**Figure 4.2.** DT IM-MS spectra of building block **1** (green,  $[M+3H]^{3+}$ ), and products **2** (blue,  $[M+2H]^{2+}$ ) and **3** (orange,  $[M+3H]^{3+}$ ) isolated from the reaction of **1** shown in Scheme 2. The collision cross sectional area ( $\text{CCS}/\text{\AA}^2$ ) distributions were calculated from the measured arrival times for the highest observed charge state of each isomer. Data shows the arrival times at a drift voltage of 50 V. Ligand strand **1**, expected to have a large degree of flexibility, exhibits the broadest distribution and largest CCS. Unknot-macrocycle **3** has a smaller CCS and narrower distribution and trefoil knot **2** displays the smallest CCS and the narrowest distribution, reflecting its compact structure and persistent size and shape.

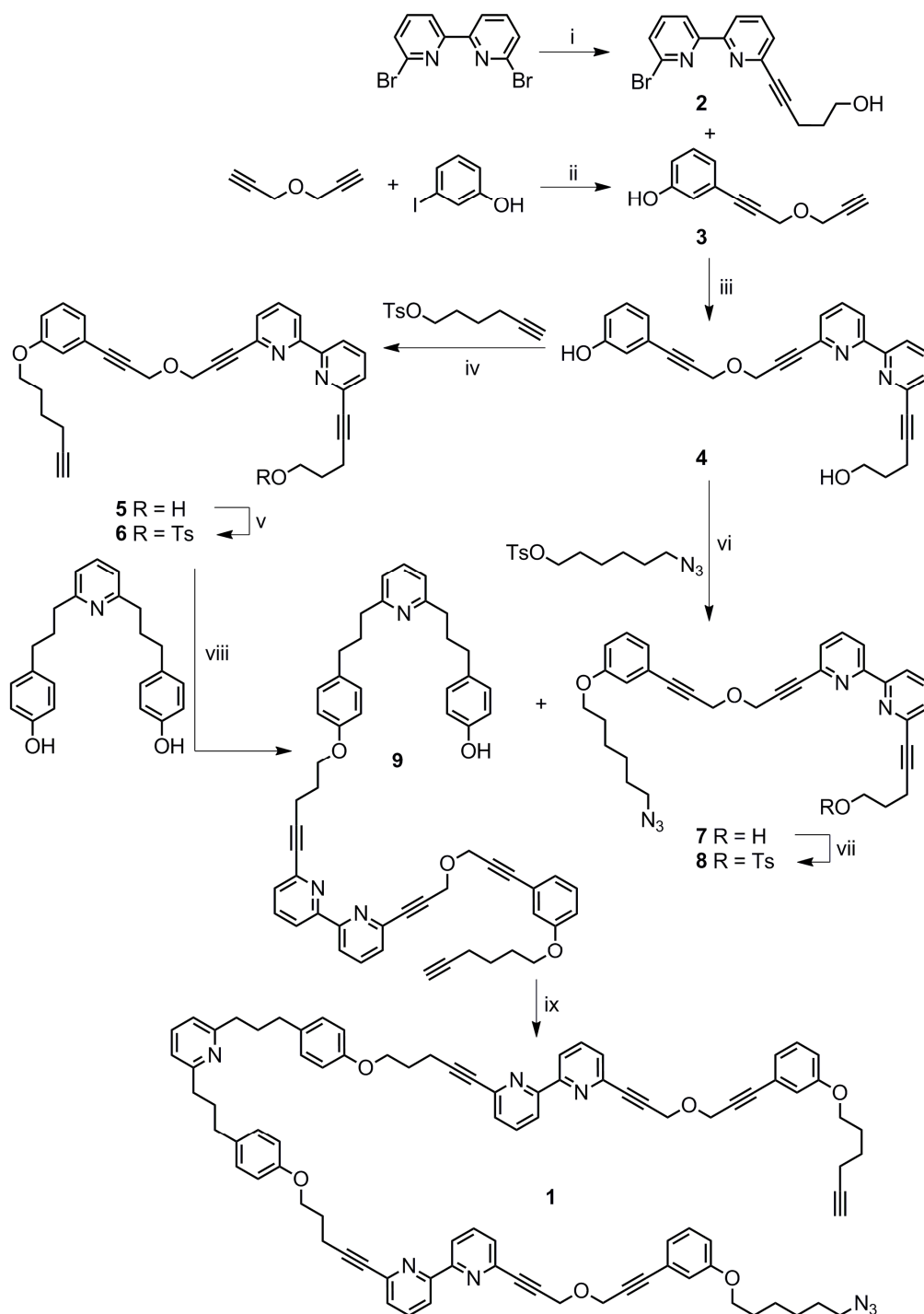
### 4.3 Conclusions

In conclusion, we have demonstrated an active template approach to the synthesis of molecular knots based upon the cooperative manipulation of a ligand with reactive end groups by two metal ions. One of the metal centers creates a loop in the ligand whilst the other catalyzes a covalent-bond-forming reaction that links the end groups through the cavity. The resulting trefoil knot and its unknot and acyclic isomers were characterized by NMR spectroscopy, mass spectrometry and DT IM-MS experiments. The latter technique is able to discriminate between the isomers through both the size and relative flexibility of their multiply-charged molecular ions. Active template strategies for entangling molecular chains, and novel methods for the structural characterization of the resulting products,<sup>22</sup> may prove useful for the synthesis of other complex molecular structures.

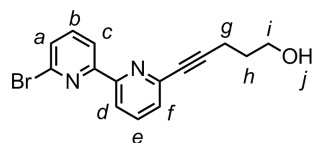
### 4.4 Experimental Section

Active template trefoil knot synthesis: In a typical procedure a solution of  $[(\text{CH}_3\text{CN})_4\text{Cu}]\text{PF}_6$  (14.7 mg, 39.4  $\mu\text{mol}$ ) in  $\text{CH}_3\text{NO}_2$  (2.5 mL) was added to a solution of **1** (35.8 mg, 26.3  $\mu\text{mol}$ ) in  $\text{CHCl}_3$  (14 mL) and  $\text{CH}_3\text{NO}_2$  (1.0 mL) and the reaction mixture was heated at 60 °C for 96 h. The solution was allowed to cool to RT, diluted with  $\text{CH}_2\text{Cl}_2$  (30 mL) and then a 17.5% aqueous solution of  $\text{NH}_3$  saturated with  $\text{Na}_2\text{EDTA}$  (30 mL) was added and the mixture stirred vigorously for 30 min. The phases were separated and the organic phase was further extracted with a 17.5% aqueous solution of  $\text{NH}_3$  saturated with  $\text{Na}_2\text{EDTA}$  (30 mL),  $\text{H}_2\text{O}$  (30 mL) and brine (30 mL), then dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure. The resulting residue was purified by size exclusion chromatography ( $\text{CH}_2\text{Cl}_2$  mobile phase) followed by preparative HPLC (reversed-phase column, gradient elution: 1. MeOH with 5→0%  $\text{H}_2\text{O}$ , 2. MeOH with 0→10%  $\text{CH}_2\text{Cl}_2$ ) to give trefoil knot **2** as a colorless film (8.6 mg, 24%) and macrocycle **3** as a yellow film (3.5 mg, 10%).

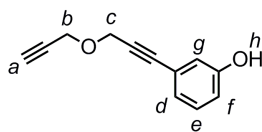
## 4.4.1. Experimental Procedures

Scheme 4.3. Synthesis of trefoil knot precursor **1**.

Reagents and conditions: (i) Pd(dppf)Cl<sub>2</sub>, Cul, Et<sub>3</sub>N, 4-pentyn-1-ol, toluene, Δ, 18 h, 52%; (ii) Pd(PPh<sub>3</sub>)<sub>4</sub>, Cul, Et<sub>3</sub>N, THF, microwave 150 W, 65 °C, 20 min, 98%; (iii) Pd(dppf)Cl<sub>2</sub>, Cul, Et<sub>3</sub>N, MeOH, microwave 150 W, 65 °C, 20 min, 38%; (iv) Cs<sub>2</sub>CO<sub>3</sub>, DMF, 60 °C, 3 h, 53%; (v) TsCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C→rt, 18 h, 81%; (vi) Cs<sub>2</sub>CO<sub>3</sub>, DMF, 60 °C, 3 h, 65%; (vii) TsCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C→rt, 18 h, 92%; (viii) Cs<sub>2</sub>CO<sub>3</sub>, DMF, 60 °C, 3 h, 54%; (ix) Cs<sub>2</sub>CO<sub>3</sub>, DMF, 60 °C, 3 h, 64%.

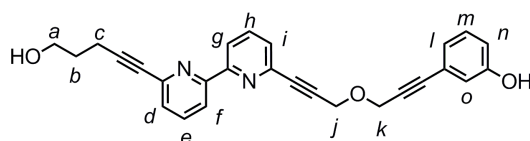
**5-(6'-Bromo-[2,2']bipyridinyl-6-yl)-pent-4-yn-1-ol****2**

6,6'-Dibromo-2,2'-bipyridine<sup>23</sup> (11.1 g, 35 mmol) was dissolved in toluene (300 mL), Et<sub>3</sub>N (200 mL) and MeOH (60 mL) and the resulting solution was degassed. Pd(dppf)Cl<sub>2</sub> (1.44 g, 1.75 mmol), CuI (672 mg, 3.5 mmol) and 4-pentyn-1-ol (3.6 mL, 39 mmol) were added and the reaction mixture heated at reflux for 18 h. The solvent was then evaporated under reduced pressure and the resulting residue was purified by column chromatography (gradient elution: 1. CH<sub>2</sub>Cl<sub>2</sub> with 5% acetone, 2. CH<sub>2</sub>Cl<sub>2</sub> with 10% acetone) to give **2** as a cream colored solid (5.9 g, 52%). M.p 83–85 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 8.42 (dd, 1H, *J* = 7.7, 0.8, H<sub>c</sub>), 8.33 (dd, 1H, *J* = 8.0, 0.9, H<sub>d</sub>), 7.76 (t, 1H, *J* = 7.8, H<sub>b</sub>), 7.66 (t, 1H, *J* = 7.8, H<sub>e</sub>), 7.49 (dd, 1H, *J* = 7.8, 0.8, H<sub>a</sub>), 7.42 (dd, 1H, *J* = 7.7, 1.0, H<sub>f</sub>), 3.86 (t, 2H, *J* = 6.1, H<sub>i</sub>), 2.62 (t, 2H, *J* = 7.0, H<sub>g</sub>), 1.97 – 1.88 (m, 2H, H<sub>h</sub>); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ = 156.6, 154.6, 143.1, 141.4, 139.1, 137.1, 128.1, 127.4, 120.3, 120.1, 90.0, 80.8, 61.6, 31.0, 16.0; LRAPCI-MS: *m/z* = 317 [M+H]<sup>+</sup>; HRESI-MS: *m/z* = 317.0285 [M+H]<sup>+</sup> (calc. for C<sub>15</sub>H<sub>14</sub>ON<sub>2</sub><sup>79</sup>Br 317.0284).

**3-(3-Prop-2-ynyloxy-prop-1-ynyl)-phenol****3**

3-Iodophenol (3.0 g, 13.6 mmol) was dissolved in THF (30 mL) and Et<sub>3</sub>N (15 mL) and the resulting solution was degassed. Pd(PPh<sub>3</sub>)<sub>4</sub> (700 mg, 0.60 mmol), CuI (228 mg, 1.2 mmol) and propargyl ether (5 mL, 48.5 mmol) were added and the reaction mixture heated at 65 °C using microwave irradiation (150W maximum) for 20 min. The solvent was then evaporated under reduced pressure and the resulting residue was purified by column chromatography (gradient elution: 1. CH<sub>2</sub>Cl<sub>2</sub>-petrol 3:1, 2. CH<sub>2</sub>Cl<sub>2</sub>) to give **3** as an orange oil (2.5 g, 98%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.18 (t, 1H, *J* = 7.9, H<sub>e</sub>), 7.03 (d, 1H, *J* = 7.6, H<sub>d</sub>), 6.92 (dd, 1H, *J* = 2.2, 1.5, H<sub>g</sub>), 6.82 (ddd, 1H, *J* = 8.1, 2.6, 0.6, H<sub>f</sub>), 4.94 (s, 1H, H<sub>h</sub>), 4.48 (s, 2H, H<sub>c</sub>), 4.32 (d, 2H, *J* = 2.4, H<sub>b</sub>), 2.48 (t, 1H *J* = 2.4 Hz, H<sub>a</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 155.2, 129.6, 124.4, 123.5, 118.3, 116.0, 86.4, 84.0, 78.8, 75.0, 57.2, 56.5; LRAPCI-MS: *m/z* = 187 [M+H]<sup>+</sup>.

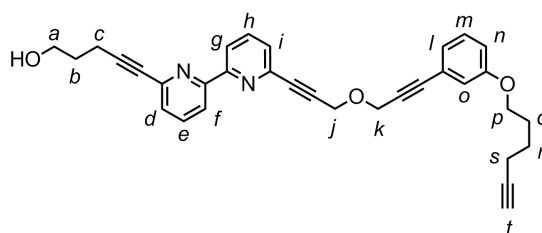
**3-(3-{3-[6'-(5-Hydroxy-pent-1-ynyl)-[2,2']bipyridinyl-6-yl]-prop-2-ynyloxy}-prop-1-ynyl)-phenol**



**4**

**2** (2.2 g, 6.93 mmol) was dissolved in MeOH (60 mL) and Et<sub>3</sub>N (30 mL) and the resulting solution was degassed. Pd(dppf)Cl<sub>2</sub> (283 mg, 346 μmol), CuI (132 mg, 692 μmol) and **3** (1.51 g, 8.12 mmol) were added and the reaction mixture heated at 65 °C using microwave irradiation (150W maximum) for 20 min. The solvent was then evaporated under reduced pressure and the resulting residue was purified by column chromatography (gradient elution: 1. CH<sub>2</sub>Cl<sub>2</sub>, 2. CH<sub>2</sub>Cl<sub>2</sub> with 5→20% acetone) to give **4** as an orange oil (1.12 g, 38%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.38 (dd, 1H, *J* = 8.0, 0.9, H<sub>g</sub>), 8.33 (dd, 1H, *J* = 8.0, 0.9 Hz, H<sub>f</sub>), 7.80 – 7.72 (m, 2H, H<sub>e</sub> + H<sub>h</sub>), 7.48 (dd, 1H, *J* = 7.7, 0.9, H<sub>i</sub>), 7.41 (dd, 1H, *J* = 7.7, 0.8, H<sub>d</sub>), 7.17 (t, 1H, *J* = 7.9, H<sub>m</sub>), 7.03 (d, 1H, *J* = 7.7, H<sub>l</sub>), 6.92 (s, 1H, H<sub>o</sub>), 6.82 (dd, 1H, *J* = 8.1, 1.9, H<sub>n</sub>), 4.59 (s, 2H, H<sub>j</sub> or H<sub>k</sub>), 4.57 (s, 2H, H<sub>j</sub> or H<sub>k</sub>), 3.86 (t, 2H, *J* = 6.1, H<sub>a</sub>), 2.61 (t, 2H, *J* = 7.0, H<sub>c</sub>), 1.96 – 1.87 (m, 2H, H<sub>b</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 155.8, 155.5, 155.4, 143.0, 141.9, 141.7, 137.1, 132.0, 129.5, 128.4, 127.5, 127.2, 124.3, 121.1, 120.4, 118.4, 116.1, 90.0, 86.2, 84.3, 84.1, 80.9, 61.6, 57.7, 57.3, 30.9, 16.0; LRAPCI-MS: *m/z* = 423 [M+H]<sup>+</sup>; HRESI-MS: *m/z* = 423.1700 [M+H]<sup>+</sup> (calc. for C<sub>27</sub>H<sub>23</sub>O<sub>3</sub>N<sub>2</sub> 423.1703).

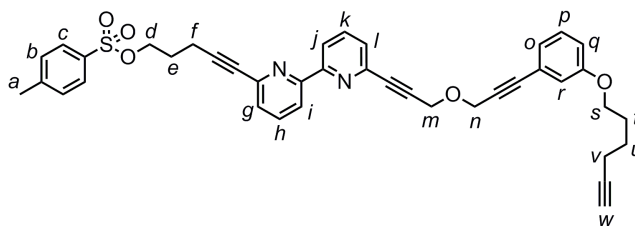
**5-(6'-{3-[3-(3-Hex-5-ynyloxy-phenyl)-prop-2-ynyloxy]-prop-1-ynyl}-[2,2']bipyridinyl-6-yl)-pent-4-yn-1-ol**



**5**

Toluene-4-sulfonic acid hex-5-ynyl ester<sup>25</sup> (735 mg, 2.91 mmol) was added to a solution of **4** (820 mg, 1.94 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (1.26 g, 3.88 mmol) in DMF (10 mL) and the reaction mixture was heated to 60 °C for 3 h. The reaction mixture was allowed to cool to RT and then diluted with EtOAc (40 mL) and H<sub>2</sub>O (40 mL). The phases were separated and the organic phase was further extracted with H<sub>2</sub>O (2 x 40 mL) and brine (2 x 40 mL) then dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (gradient elution: CH<sub>2</sub>Cl<sub>2</sub> with 2→10% acetone) to give **5** as an orange oil (518 mg, 53%).<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.44 (d, 1H, *J* = 7.1, H<sub>g</sub>), 8.37 (d, 1H, *J* = 7.1, H<sub>f</sub>), 7.81 – 7.72 (m, 2H, H<sub>e</sub> + H<sub>h</sub>), 7.51 – 7.46 (m, 1H, H<sub>i</sub>), 7.44 – 7.39 (m, 1H, H<sub>d</sub>), 7.23 – 7.17 (m, 1H, H<sub>m</sub>), 7.05 (d, 1H, *J* = 7.6, H<sub>l</sub>), 6.99 (d, 1H, *J* = 2.5, H<sub>o</sub>), 6.87 (dd, 1H, *J* = 7.9, 2.1, H<sub>n</sub>), 4.61 (s, 2H, H<sub>j</sub> or H<sub>k</sub>), 4.58 (s, 2H, H<sub>j</sub> or H<sub>k</sub>), 3.97 (t, 2H, *J* = 6.3 Hz, H<sub>p</sub>), 3.86 (t, 2H, *J* = 6.1, H<sub>a</sub>), 2.62 (t, 2H, *J* = 7.0, H<sub>c</sub>), 2.27 (td, 2H, *J*<sub>d</sub> = 7.0, *J*<sub>t</sub> = 2.6, H<sub>s</sub>), 1.97 (t, 1H, *J* = 2.6, H<sub>t</sub>), 1.96 – 1.85 (m, 4H, H<sub>b</sub> + H<sub>q</sub>), 1.76 – 1.66 (m, 2H, H<sub>r</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 158.6, 155.8, 155.4, 142.9, 141.8, 137.0, 137.0, 129.3, 127.5, 127.2, 124.2, 123.2, 121.0, 120.3, 117.1, 115.7, 89.9, 86.9, 86.1, 84.2, 83.9, 83.9, 80.9, 68.6, 67.2, 61.6, 57.6, 57.2, 30.9, 28.1, 24.9, 18.0, 16.0; LRAPCI-MS: *m/z* = 503 [M+H]<sup>+</sup>; HRESI-MS: *m/z* = 503.2330 [M+H]<sup>+</sup> (calc. for C<sub>33</sub>H<sub>31</sub>O<sub>3</sub>N<sub>2</sub> 503.2329).

**Toluene-4-sulfonic acid 5-(6'-{3-[3-(3-hex-5-ynyloxy-phenyl)-prop-2-ynyloxy]-prop-1-ynyl}-[2,2']bipyridinyl-6-yl)-pent-4-ynyl ester**

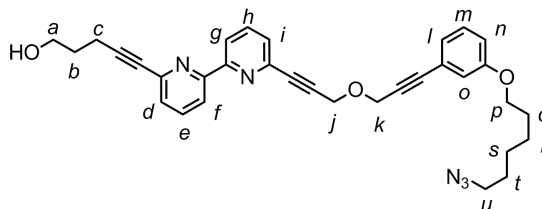


## 6

To a solution of **5** (345 mg, 686  $\mu$ mol) and  $\text{Et}_3\text{N}$  (190  $\mu$ L, 1.4 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) at 0  $^\circ\text{C}$  was added *p*-toluenesulfonyl chloride (144 mg, 755  $\mu$ mol) and the reaction allowed to stir at RT for 18 h. The crude reaction mixture was concentrated under reduced pressure and the resulting residue purified by column chromatography (gradient elution: 1. 3:1 petrol- $\text{CH}_2\text{Cl}_2$ , 2. 3:1:1 petrol- $\text{CH}_2\text{Cl}_2$ -EtOAc) to give **6** as a yellow oil (366 mg, 81%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.41 – 8.33 (m, 2H,  $\text{H}_i + \text{H}_j$ ), 7.80 (d, 2H,  $J = 8.3$ ,  $\text{H}_c$ ), 7.78 – 7.70 (m, 2H,  $\text{H}_h + \text{H}_k$ ), 7.47 (d, 1H,  $J = 7.6$ ,  $\text{H}_l$ ), 7.31 (d, 1H,  $J = 7.6$ ,  $\text{H}_g$ ), 7.28 (d, 2H,  $J = 8.1$ ,  $\text{H}_b$ ), 7.19 (t, 1H,  $J = 7.9$ ,  $\text{H}_p$ ), 7.03 (d, 1H,  $J = 7.6$ ,  $\text{H}_o$ ), 6.97 (d, 1H,  $J = 2.1$ ,  $\text{H}_r$ ), 6.86 (dd, 1H,  $J = 8.3$ , 2.4,  $\text{H}_q$ ), 4.59 (s, 2H,  $\text{H}_m$  or  $\text{H}_n$ ), 4.57 (s, 2H,  $\text{H}_m$  or  $\text{H}_n$ ), 4.21 (t, 2H,  $J = 6.0$ ,  $\text{H}_d$ ), 3.95 (t, 2H,  $J = 6.3$ ,  $\text{H}_s$ ), 2.54 (t, 2H,  $J = 6.9$ ,  $\text{H}_f$ ), 2.34 (s, 3H,  $\text{H}_a$ ), 2.25 (td, 2H,  $J_d = 7.0$ ,  $J_t = 2.6$ ,  $\text{H}_v$ ), 2.02 – 1.93 (m, 3H,  $\text{H}_e + \text{H}_w$ ), 1.88 (m, 2H,  $\text{H}_t$ ), 1.76 – 1.64 (m, 2H,  $\text{H}_u$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 158.5, 155.7, 155.4, 144.7, 142.6, 141.8, 137.0, 136.9, 132.7, 129.7, 129.3, 127.8, 127.4, 127.2, 124.1, 123.2, 120.9, 120.3, 117.0, 115.6, 87.9, 86.8, 86.1, 84.2, 83.9, 83.8, 81.4, 68.7, 68.6, 67.2, 57.6, 57.1, 28.0, 27.4, 24.8, 21.5, 18.0, 15.6; LRAPCI-MS:  $m/z$  = 657  $[\text{M}+\text{H}]^+$ ; HRESI-MS:  $m/z$  = 657.2419  $[\text{M}+\text{H}]^+$  (calc. for  $\text{C}_{40}\text{H}_{37}\text{O}_5\text{N}_2\text{S}$  657.2418).



**5-[6'-(3-{3-[3-(6-Azido-hexyloxy)-phenyl]-prop-2-ynyloxy}-prop-1-ynyl)-[2,2']bipyridinyl-6-yl]-pent-4-yn-1-ol**



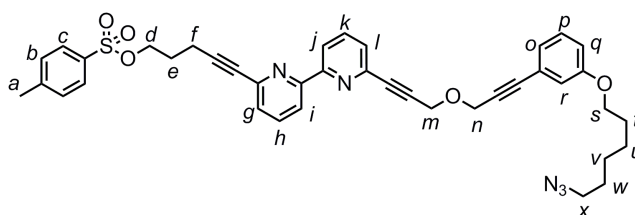
**7**

Toluene-4-sulfonic acid 6-azido-hexyl ester<sup>26</sup> (535 mg, 1.8 mmol) was added to a solution of **4** (507 mg, 1.2 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (782 mg, 2.4 mmol) in DMF (10 mL) and the reaction mixture was heated to 60 °C for 3 h. The reaction mixture was allowed to cool to RT and then diluted with EtOAc (40 mL) and H<sub>2</sub>O (40 mL). The phases were separated and the organic phase was further extracted with H<sub>2</sub>O (2 x 40 mL) and brine (2 x 40 mL) then dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (gradient elution: 1. CH<sub>2</sub>Cl<sub>2</sub> with 2% acetone, 2. CH<sub>2</sub>Cl<sub>2</sub> with 5% acetone) to give **7** as an orange oil (430 mg, 65%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.43 (d, 1H, *J* = 8.0, H<sub>g</sub>), 8.37 (d, 1H, *J* = 7.9, H<sub>f</sub>), 7.81 – 7.72 (m, 2H, H<sub>e</sub> + H<sub>h</sub>), 7.48 (d, 1H, *J* = 7.6, H<sub>i</sub>), 7.41 (d, 1H, *J* = 7.7, H<sub>d</sub>), 7.23 – 7.18 (m, 1H, H<sub>m</sub>), 7.05 (dt, 1H, *J* = 7.6, 1.1, H<sub>l</sub>), 6.98 (dd, 1H, *J* = 2.4, 1.4, H<sub>o</sub>), 6.87 (ddd, 1H, *J* = 8.3, 2.6, 0.8, H<sub>n</sub>), 4.60 (s, 2H, H<sub>j</sub> or H<sub>k</sub>), 4.58 (s, 2H, H<sub>j</sub> or H<sub>k</sub>), 3.94 (t, 2H, *J* = 6.4 Hz, H<sub>p</sub>), 3.85 (t, 2H, *J* = 6.1, H<sub>a</sub>), 3.28 (t, 2H, *J* = 6.9, H<sub>u</sub>), 2.62 (t, 2H, *J* = 7.0, H<sub>c</sub>), 1.93 (p, 2H, *J* = 6.6, H<sub>b</sub>), 1.83 – 1.73 (m, 2H, H<sub>q</sub>), 1.68 – 1.58 (m, 2H, H<sub>t</sub>), 1.54 – 1.39 (m, 4H, H<sub>r</sub> + H<sub>s</sub>);

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ = 158.7, 155.8, 155.5, 142.9, 141.9, 137.0, 137.0, 129.3, 127.5, 127.2, 124.2, 123.3, 121.1, 120.3, 117.1, 115.7, 89.9, 86.9, 86.2, 84.2, 83.9, 80.9, 67.7, 61.7, 57.6, 57.2, 51.3, 31.0, 29.0, 28.7, 26.4, 25.6, 16.0; LRAPCI-MS: *m/z* = 548 [M+H]<sup>+</sup>; HRESI-MS: *m/z* = 548.2675 [M+H]<sup>+</sup> (calc. for C<sub>33</sub>H<sub>34</sub>O<sub>3</sub>N<sub>5</sub> 548.2656).

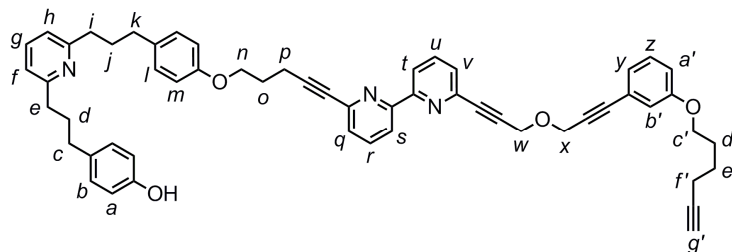
**Toluene-4-sulfonic acid 5-[6'-(3-{3-[3-(6-azido-hexyloxy)-phenyl]-prop-2-ynyloxy}-prop-1-ynyl)-[2,2']bipyridinyl-6-yl]-pent-4-ynyl ester**



**8**

To a solution of **7** (244 mg, 450  $\mu$ mol) and  $\text{Et}_3\text{N}$  (130  $\mu$ L, 0.9 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) at 0 °C was added *p*-toluenesulfonyl chloride (93 mg, 490  $\mu$ mol) and the reaction allowed to stir at RT for 18 h. The crude reaction mixture was concentrated under reduced pressure and the resulting residue purified by column chromatography (gradient elution: 1.  $\text{CH}_2\text{Cl}_2$ , 2.  $\text{CH}_2\text{Cl}_2$  with 2% acetone) to give **8** as an orange oil (288 mg, 92%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.43 – 8.34 (m, 2H,  $\text{H}_i + \text{H}_j$ ), 7.81 (d, 2H,  $J = 8.3$ ,  $\text{H}_c$ ), 7.78 (t, 1H,  $J = 7.0$ ,  $\text{H}_k$ ), 7.74 (t, 1H,  $J = 7.0$ ,  $\text{H}_h$ ), 7.48 (dd, 1H,  $J = 7.7$ , 1.0,  $\text{H}_l$ ), 7.33 (dd, 1H,  $J = 7.7$ , 1.0,  $\text{H}_g$ ), 7.30 (d, 2H,  $J = 7.9$ ,  $\text{H}_b$ ), 7.23 – 7.18 (m, 1H,  $\text{H}_p$ ), 7.05 (dt, 1H,  $J_d = 7.6$ ,  $J_t = 1.1$ ,  $\text{H}_o$ ), 6.98 (dd, 1H,  $J = 2.4$ , 1.4,  $\text{H}_r$ ), 6.87 (ddd, 1H,  $J = 8.3$ , 2.6, 0.9,  $\text{H}_q$ ), 4.61 (s, 2H,  $\text{H}_m$  or  $\text{H}_n$ ), 4.58 (s, 2H,  $\text{H}_m$  or  $\text{H}_n$ ), 4.23 (t, 2H,  $J = 6.0$ ,  $\text{H}_d$ ), 3.94 (t, 2H,  $J = 6.4$ ,  $\text{H}_s$ ), 3.28 (t, 2H,  $J = 6.9$ ,  $\text{H}_x$ ), 2.55 (t, 2H,  $J = 6.9$ ,  $\text{H}_f$ ), 2.36 (s, 3H,  $\text{H}_a$ ), 2.04 – 1.96 (m, 2H,  $\text{H}_e$ ), 1.82 – 1.74 (m, 2H,  $\text{H}_t$ ), 1.68 – 1.59 (m, 2H,  $\text{H}_w$ ), 1.54 – 1.39 (m, 4H,  $\text{H}_u + \text{H}_v$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta = 158.7$ , 155.7, 155.4, 144.7, 142.6, 141.9, 137.1, 137.0, 132.8, 129.8, 129.3, 127.9, 127.5, 127.3, 124.1, 123.3, 121.0, 120.5, 117.1, 115.7, 88.2, 86.9, 86.1, 84.3, 83.9, 81.4, 68.8, 67.7, 57.7, 57.2, 51.3, 29.0, 28.7, 27.5, 26.4, 25.6, 21.5, 15.7; LRAPCI-MS:  $m/z = 702$   $[\text{M}+\text{H}]^+$ ; HRESI-MS:  $m/z = 702.2734$   $[\text{M}+\text{H}]^+$  (calc. for  $\text{C}_{40}\text{H}_{40}\text{O}_5\text{N}_5\text{S}$  702.2745).

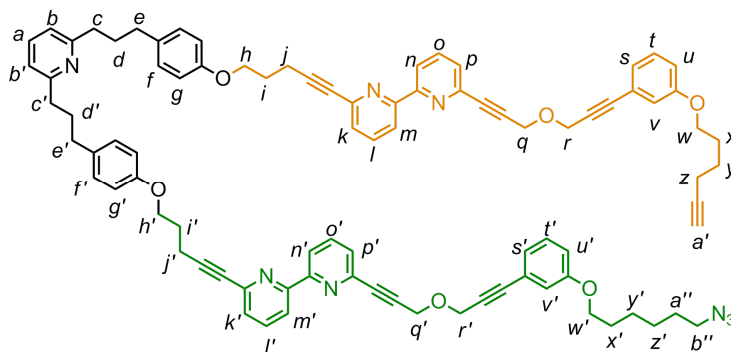
**4-{3-[6-(3-{4-[5-(6'-{3-[3-(4-Hex-5-ynyloxy-phenyl)-prop-2-ynyloxy]-prop-1-ynyl}-[2,2']bipyridinyl-6-yl)-pent-4-ynyloxy]-phenyl)-propyl)-pyridin-2-yl]-propyl}-phenol**



**9**

**6** (152 mg, 231  $\mu\text{mol}$ ) was added to a solution of 2,6-bis(3-(4-hydroxyphenyl)-propyl)-pyridine<sup>24</sup> (241 mg, 694  $\mu\text{mol}$ ) and  $\text{Cs}_2\text{CO}_3$  (226 mg, 694  $\mu\text{mol}$ ) in DMF (10 mL) and the reaction mixture was heated to 60 °C for 2 h. The reaction mixture was allowed to cool to RT and then diluted with EtOAc (40 mL) and  $\text{H}_2\text{O}$  (40 mL). The phases were separated and the organic phase was further extracted with  $\text{H}_2\text{O}$  (2 x 40 mL) and brine (2 x 40 mL) then dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (gradient elution: 1.  $\text{CH}_2\text{Cl}_2$  with 2% acetone, 2.  $\text{CH}_2\text{Cl}_2$  with 4% acetone) to give **9** as a yellow oil (103 mg, 54%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.40 (dd, 1H,  $J = 8.0, 0.9$ ,  $\text{H}_t$ ), 8.35 (dd, 1H,  $J = 8.0, 0.9$ ,  $\text{H}_s$ ), 7.78 – 7.70 (m, 2H,  $\text{H}_r + \text{H}_u$ ), 7.50 (t, 1H,  $J = 7.7$ ,  $\text{H}_g$ ), 7.47 (dd, 1H,  $J = 7.7, 0.9$ ,  $\text{H}_v$ ), 7.39 (dd, 1H,  $J = 7.7, 0.8$ ,  $\text{H}_q$ ), 7.21 (t, 1H,  $J = 8.0$ ,  $\text{H}_z$ ), 7.07 – 7.00 (m, 3H,  $\text{H}_l + \text{H}_y$ ), 7.00 – 6.92 (m, 5H,  $\text{H}_f + \text{H}_h + \text{H}_m + \text{H}_b$ ), 6.87 (dd, 1H,  $J = 8.3, 1.9$ ,  $\text{H}_{a'}$ ), 6.79 (d, 2H,  $J = 8.6$ ,  $\text{H}_b$ ), 6.67 (d, 2H,  $J = 8.5$ ,  $\text{H}_a$ ), 4.60 (s, 2H,  $\text{H}_w$  or  $\text{H}_x$ ), 4.57 (s, 2H,  $\text{H}_w$  or  $\text{H}_x$ ), 4.08 (t, 2H,  $J = 6.0$ ,  $\text{H}_n$ ), 3.96 (t, 2H,  $J = 6.3$ ,  $\text{H}_{c'}$ ), 2.83 – 2.74 (m, 4H,  $\text{H}_e + \text{H}_i$ ), 2.68 (t, 2H,  $J = 7.0$ ,  $\text{H}_p$ ), 2.64 – 2.53 (m, 4H,  $\text{H}_c + \text{H}_k$ ), 2.27 (td, 2H  $J_t = 7.0$ ,  $J_d = 2.6$ ,  $\text{H}_f$ ), 2.14 – 2.06 (m, 2H,  $\text{H}_o$ ), 2.04 – 1.85 (m, 6H,  $\text{H}_d + \text{H}_j + \text{H}_{d'}$ ), 1.70 (m, 2H,  $\text{H}_{e'}$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 161.4, 161.3, 158.6, 156.8, 155.8, 155.4, 154.3, 143.0, 141.8, 137.1, 137.0, 136.8, 134.3, 133.2, 129.3, 129.3, 127.5, 127.3, 127.2, 124.2, 123.2, 121.1, 121.1, 120.4, 120.0, 117.1, 115.7, 115.1, 114.2, 89.9, 86.9, 86.1, 84.3, 84.0, 83.9, 80.8, 68.6, 67.2, 66.2, 61.6, 57.6, 57.2, 37.5, 34.6, 34.5, 32.0, 31.8, 29.6, 28.1,$

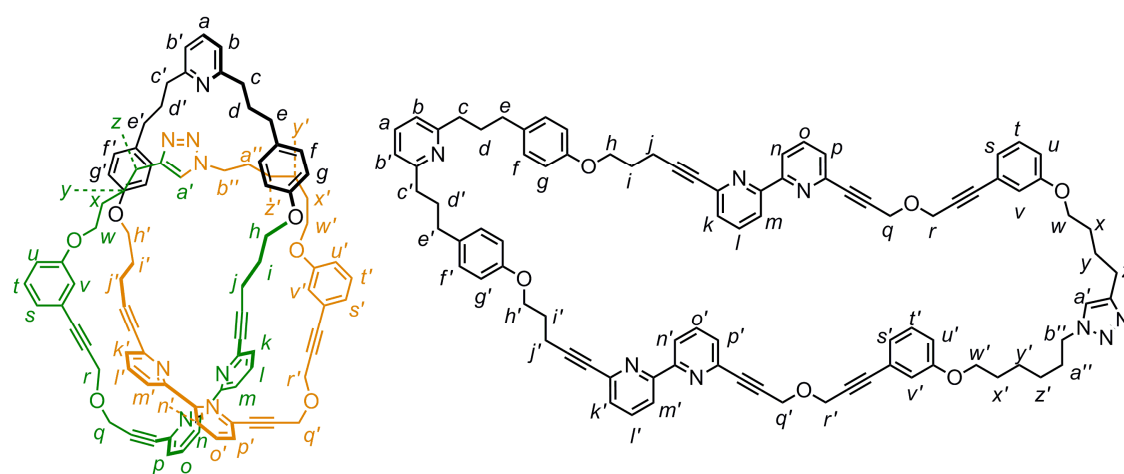
24.9, 18.0, 16.2; LRAPCI-MS:  $m/z = 832 [M+H]^+$ ; HRESI-MS:  $m/z = 832.4095 [M+H]^+$  (calc. for  $C_{56}H_{54}O_4N_3$  832.4109).



# 1

**8** (288 mg, 410  $\mu$ mol) was added to a solution of **9** (180 mg, 216  $\mu$ mol) and  $Cs_2CO_3$  (141 mg, 432  $\mu$ mol) in DMF (2.5 mL) and the reaction mixture was heated to 60  $^{\circ}C$  for 3 h. The reaction mixture was allowed to cool to RT and then diluted with EtOAc (10 mL) and  $H_2O$  (10 mL). The phases were separated and the organic phase was further extracted with  $H_2O$  (2 x 10 mL) and brine (2 x 10 mL) then dried ( $MgSO_4$ ) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (gradient elution:  $CH_2Cl_2$  with 1 $\rightarrow$ 4% EtOAc) to give **1** as a yellow oil (187 mg, 64%).  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  8.42 (d, 2H,  $J = 8.0$ ,  $H_n + H_{n'}$ ), 8.36 (d, 2H,  $J = 7.9$ ,  $H_m + H_{m'}$ ), 7.78 – 7.69 (m, 4H,  $H_l + H_o + H_{l'} + H_{o'}$ ), 7.50 – 7.44 (m, 3H,  $H_a + H_p + H_{p'}$ ), 7.39 (d, 2H,  $J = 7.6$ ,  $H_k + H_{k'}$ ), 7.20 (t, 2H,  $J = 8.0$ ,  $H_t + H_{t'}$ ), 7.09 (t, 4H,  $J = 7.1$ ,  $H_f + H_{f'}$ ), 7.05 (d, 2H,  $J = 7.6$ ,  $H_s + H_{s'}$ ), 6.98 (s, 2H,  $H_v + H_{v'}$ ), 6.93 (d, 2H,  $J = 7.7$ ,  $H_b + H_{b'}$ ), 6.90 – 6.81 (m, 6H,  $H_g + H_u + H_{g'} + H_{u'}$ ), 4.60 (s, 4H,  $H_q$  or  $H_r + H_{q'}$  or  $H_{r'}$ ), 4.57 (s, 4H,  $H_q$  or  $H_r + H_{q'}$  or  $H_{r'}$ ), 4.10 (t, 4H,  $J = 6.0$ ,  $H_h + H_{h'}$ ), 3.98 – 3.90 (m, 4H,  $H_w + H_{w'}$ ), 3.27 (t, 2H,  $J = 6.9$ ,  $H_{b''}$ ), 2.82 – 2.75 (m, 4H,  $H_c + H_{c'}$ ), 2.69 (t, 4H,  $J = 7.0$ ,  $H_j + H_{j'}$ ), 2.65 – 2.58 (m, 4H,  $H_e + H_{e'}$ ), 2.27 (td, 2H,  $J_t = 7.0$ ,  $J_d = 2.6$ ,  $H_z$ ), 2.17 – 2.08 (m, 4H,  $H_i + H_{i'}$ ), 2.03 – 1.94 (m, 5H,  $H_d + H_{a'} + H_{d'}$ ), 1.94 – 1.83 (m, 2H,  $H_x$ ), 1.82 – 1.73 (m, 2H,  $H_{x'}$ ), 1.73 – 1.56 (m, 4H,  $H_y + H_{a''}$ ), 1.53 – 1.35 (m, 4H,  $H_{y'} + H_{z'}$ );  $^{13}C$  NMR (100 MHz,  $CDCl_3$ ):  $\delta$  = 161.3 (2xC), 158.6, 158.6, 156.9 (2xC), 155.8 (2xC), 155.4 (2xC), 142.9 (2xC), 141.8

(2xC), 137.0 (2xC), 136.9 (2xC), 136.4 (2xC), 134.4 (2xC), 129.3 (2xC), 127.5, 127.4 (2xC), 127.3 (2xC), 124.1, 124.1, 123.2 (2xC), 121.0 (2xC), 120.2 (2xC), 119.7 (2xC), 117.0 (2xC), 115.7 (2xC), 114.3 (2xC), 89.7 (2xC), 86.9, 86.9, 86.1 (2xC), 84.1 (2xC), 83.9 (2xC), 83.9, 80.9 (2xC), 68.6 (2xC), 67.6, 67.2, 66.2, 57.6 (2xC), 57.2 (2xC), 51.2, 37.9 (2xC), 34.6 (2xC), 31.9 (2xC), 29.5, 28.9, 28.7, 28.1, 28.0, 26.4, 25.5, 24.9, 18.0, 16.2 (2xC); LRESI-MS:  $m/z = 1362 [M+H]^+$ ; HRESI-MS:  $m/z = 1361.6613 [M+H]^+$  (calc. for  $C_{88}H_{85}N_8O_6$  1361.6597).



**Trefoil knot 2 and macrocycle 3**

A solution of  $[(CH_3CN)_4Cu]PF_6$  (14.7 mg, 39.4  $\mu$ mol) in  $CH_3NO_2$  (2.5 mL) was added to a solution of **1** (35.8 mg, 26.3  $\mu$ mol) in  $CHCl_3$  (14 mL) and  $CH_3NO_2$  (1.0 mL) and the reaction mixture was heated to 60 °C for 96 h. The reaction mixture was allowed to cool to RT, diluted with  $CH_2Cl_2$  (30 mL) then a 17.5% aqueous solution of  $NH_3$  saturated with  $Na_2EDTA$  (30 mL) was added and stirred vigorously for 30 min. The phases were separated and the organic phase was further extracted with a 17.5% aqueous solution of  $NH_3$  saturated with  $Na_2EDTA$  (30 mL),  $H_2O$  (30 mL) and brine (30 mL) then dried ( $MgSO_4$ ) and concentrated under reduced pressure. The resulting residue was purified by size exclusion chromatography ( $CH_2Cl_2$  mobile phase) followed by preparative HPLC (reversed-phase column, gradient elution: 1. MeOH

with 5→0% H<sub>2</sub>O, 2. MeOH with 0→10% CH<sub>2</sub>Cl<sub>2</sub>) to give trefoil knot **2** as a colorless film (8.6 mg, 24%) and macrocycle **3** as a yellow film (3.5 mg, 10%).

### Trefoil knot **2**

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) partially assigned  $\delta$  8.56 (dd,  $J = 7.9, 0.7$ , 1H), 8.46 (d,  $J = 8.9$ , 1H), 8.37 (d,  $J = 7.9$ , 1H), 8.31 (dd,  $J = 7.9, 0.9$ , 1H), 8.13 (d,  $J = 8.9$ , 1H), 7.98 (s, 1H), 7.79 (t,  $J = 7.8$ , 1H), 7.75 – 7.66 (m, 2H), 7.42 (dt,  $J = 11.6, 10.5$ , 4H), 7.35 (d,  $J = 7.5$ , 1H), 7.27 (s, 1H, H<sub>a</sub><sup>+</sup>), 7.21 – 7.14 (m, 2H, H<sub>t</sub> + H<sub>t</sub><sup>+</sup>), 7.07 (dd,  $J = 8.6, 2.2$ , 5H), 7.02 (d,  $J = 7.6$ , 1H), 6.98 (dd,  $J = 8.3, 1.9$ , 1H), 6.95 (dd,  $J = 2.3, 1.4$ , 1H), 6.92 (d,  $J = 7.6$ , 2H), 6.87 – 6.85 (m, 1H), 6.85 – 6.77 (m, 6H), 5.33 (s, 2H, H<sub>q</sub> or H<sub>r</sub> or H<sub>q</sub><sup>+</sup> or H<sub>r</sub><sup>+</sup>), 5.07 (AB, 2H, H<sub>q</sub> or H<sub>r</sub> or H<sub>q</sub><sup>+</sup> or H<sub>r</sub><sup>+</sup>,  $J = 13.2$ ), 4.59 (s, 2H, H, H<sub>q</sub> or H<sub>r</sub> or H<sub>q</sub><sup>+</sup> or H<sub>r</sub><sup>+</sup>), 4.56 (s, 2H, H<sub>q</sub> or H<sub>r</sub> or H<sub>q</sub><sup>+</sup> or H<sub>r</sub><sup>+</sup>), 4.30 (t,  $J = 7.1$ , 2H, H<sub>s</sub><sup>+</sup>), 4.14 – 4.06 (m, 4H, H<sub>h</sub> + H<sub>h</sub><sup>+</sup>), 4.00 (t,  $J = 4.9$ , 2H), 3.88 (t,  $J = 6.3$ , 2H), 2.79 (br, 4H), 2.72 – 2.65 (m, 6H), 2.14 – 2.06 (m, 6H), 1.93 – 1.84 (m, 6H), 1.76 – 1.69 (m, 2H), 1.50 – 1.41 (m, 2H), 1.39 – 1.26 (m, 8H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta = 159.2$  (2xC), 158.6 (2xC), 156.4 (2xC), 155.9 (2xC), 155.5, 155.1, 148.2, 147.8, 143.1, 141.9, 141.7, 138.2, 137.6, 137.1, 137.0, 134.7 (2xC), 132.4 (2xC), 129.9 (2xC), 129.4 (2xC), 127.5, 127.4, 127.3, 126.6, 124.2, 123.4, 121.7, 121.1, 120.6, 120.6, 120.5, 120.3, 118.9, 117.2, 115.8, 115.5, 114.5, 114.5, 114.4, 114.2, 89.7, 89.6, 87.0, 86.3 (2xC), 84.3, 84.0, 81.2, 81.1, 73.3, 72.7, 67.7, 67.6, 66.3, 66.2, 65.0, 57.7, 57.3, 53.4, 50.9, 50.0, 31.9, 30.2, 29.7, 29.7, 29.4, 28.8, 28.8, 28.2, 27.9, 26.1, 26.0, 25.4, 25.4, 22.7, 16.3, 16.1, 14.1; LRESI-MS:  $m/z = 1362$  [M+H]<sup>+</sup>; HRESI-MS:  $m/z = 1361.6601$  [M+H]<sup>+</sup> (calc. for calc. for C<sub>88</sub>H<sub>85</sub>N<sub>8</sub>O<sub>6</sub> 1361.6597).

### Macrocycle **3**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.39 (d,  $J = 7.9$ , 2H, H<sub>n</sub> + H<sub>n</sub><sup>+</sup>), 8.33 (d,  $J = 7.8$ , 2H, H<sub>m</sub> + H<sub>m</sub><sup>+</sup>), 7.77 – 7.66 (m, 4H, H<sub>i</sub> + H<sub>o</sub> + H<sub>i</sub><sup>+</sup> + H<sub>o</sub><sup>+</sup>), 7.50 – 7.40 (m, 3H, H<sub>a</sub> + H<sub>p</sub> + H<sub>p</sub><sup>+</sup>), 7.37 (d,  $J = 7.0$ , 2H, H<sub>k</sub> + H<sub>k</sub><sup>+</sup>), 7.25 (s, 1H, H<sub>a</sub>), 7.21 – 7.16 (m, 2H, H<sub>t</sub> + H<sub>t</sub><sup>+</sup>), 7.08 (d,  $J = 8.6$ , 4H, H<sub>f</sub> + H<sub>f</sub><sup>+</sup>), 7.03 (d,  $J = 7.6$ , 2H, H<sub>s</sub> + H<sub>s</sub><sup>+</sup>), 6.96 (dd,  $J = 3.8, 2.6$ , 2H, H<sub>v</sub> + H<sub>v</sub><sup>+</sup>), 6.93 (d,  $J = 7.6$ , 2H, H<sub>b</sub> + H<sub>b</sub><sup>+</sup>), 6.88 – 6.80 (m, 6H, H<sub>g</sub> + H<sub>u</sub> + H<sub>g</sub><sup>+</sup> + H<sub>u</sub><sup>+</sup>), 4.59 (s, 4H, H<sub>q</sub> or H<sub>r</sub> + H<sub>q</sub><sup>+</sup> or H<sub>r</sub><sup>+</sup>), 4.57 (s, 4H, H<sub>q</sub> or H<sub>r</sub> + H<sub>q</sub><sup>+</sup> or H<sub>r</sub><sup>+</sup>), 4.30 (t,  $J = 7.1$ , 2H, H<sub>b</sub><sup>+</sup>), 4.11 (t,  $J = 6.0$ , 4H, H<sub>h</sub> +

$H_h$ ), 3.98 – 3.87 (m, 4H,  $H_w + H_w'$ ), 2.82 – 2.72 (m, 6H,  $H_c + H_z + H_c'$ ), 2.68 (t,  $J = 6.9$ , 4H,  $H_j + H_j'$ ), 2.64 – 2.55 (m, 4H,  $H_e + H_e'$ ), 2.15 – 2.05 (m, 4H,  $H_i + H_i'$ ), 2.06 – 1.94 (m, 4H,  $H_d + H_d'$ ), 1.94 – 1.85 (m, 2H,  $H_x$ ), 1.85 – 1.78 (m, 4H,  $H_x' + H_a''$ ), 1.78 – 1.69 (m, 2H,  $H_y$ ), 1.52 – 1.31 (m, 4H,  $H_x' + H_y'$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 161.3$  (2xC), 158.6 (2xC), 156.9 (2xC), 155.9 (2xC), 155.5 (2xC), 147.8, 143.00 (2xC), 141.9 (2xC), 137.5 (2xC), 137.1 (2xC), 137.0 (2xC), 134.8 (2xC), 129.4 (2xC), 129.3 (2xC), 127.5, 127.3, 124.2, 124.2, 123.3, 123.3, 121.1 (2xC), 120.6 (2xC), 120.4 (2xC), 117.3 (2xC), 117.2 (2xC), 115.7, 115.7, 114.4 (2xC), 89.7 (2xC), 87.0, 86.2 (2xC), 84.3 (2xC), 84.0 (2xC), 81.0 (2xC), 67.6 (2xC), 67.5, 66.3, 65.0, 57.7 (2xC), 57.2 (2xC), 50.0, 31.9 (2xC), 30.0 (2xC), 29.6 (2xC), 28.8, 28.6, 28.0, 26.1, 25.9, 25.4, 25.2, 22.7, 16.1, 14.1 (2xC); LRESI-MS:  $m/z = 1362$   $[\text{M}+\text{H}]^+$ ; HRESI-MS:  $m/z = 1361.6603$   $[\text{M}+\text{H}]^+$  (calc. for calc. for  $\text{C}_{88}\text{H}_{85}\text{N}_8\text{O}_6$  1361.6597).

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15. Molecular modeling was carried using the SPARTAN package. W. J. Hehre, SPARTAN '06, 1.1; Wavefunction, Inc.: Irvine, CA 92612, 2006.
16. Upon adding  $[(\text{CH}_3\text{CN})_4\text{Cu}]\text{PF}_6$  to a solution of **1** in chloroform a red, gummy solid formed instantaneously. The solid was insoluble in all common laboratory solvents so was assumed to be a result of rapid polymerization.
17. The use of less than a stoichiometric amount of copper is to try to minimize the amount of  $\text{Cu}^{\text{I}}$  not coordinated to **1**. “Free”  $\text{Cu}^{\text{I}}$  could catalyze the CuAAC reaction without the end groups passing through the ligand strand loop, generating unknot macrocycle **3**.  $\text{Cu}^{\text{I}}$  can turn over during active template CuAAC reactions [ref 12a,d,i,l] and so stoichiometric amounts of the metal are unnecessary.
18. The assignment is confirmed as an AB system by a coupling constant value ( $J_{\text{AB}} = 13.2 \text{ Hz}$ ) that is unchanged when measured at 500 MHz (Figure 4.2d) and 400 MHz (Figure 4.2e) and  $^1\text{H}$ - $^1\text{H}$  COSY experiments that show that the two protons coupled in the signal are not coupled to other protons in the molecule.
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## **Chapter 5**

# **A hybrid organic-inorganic catenane**

Prepared for publication as '*A hybrid organic-inorganic catenane*' Beatriz Ballesteros, David A. Leigh, Tao Long, David Schultz, Jenny Wu and Richard E. P. Winpenny.

**Synopsis**

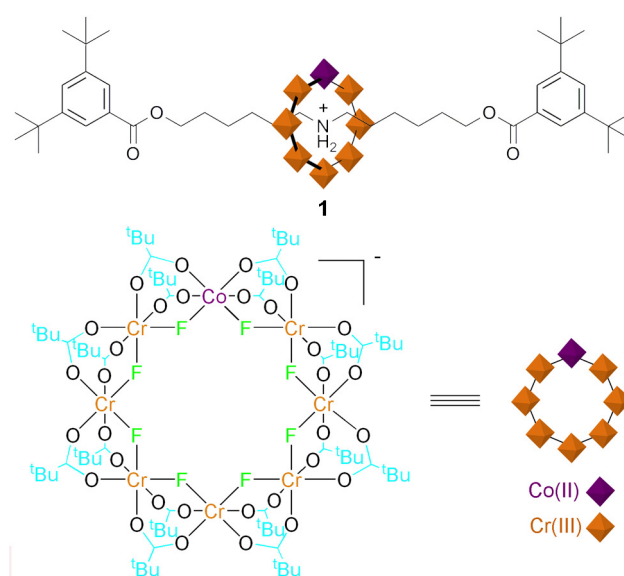
*The synthesis and characterization of a hybrid organic–inorganic [2]catenane is described. The organic macrocycle features a dialkylammonium unit that templates the formation of the heterometallic octa- $[\text{Cr}_7\text{CoF}_8(\text{O}_2\text{CtBu})_{16}]$  nuclear cage to give the interlocked structure through a macrocyclization strategie.*

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## 5.1 Introduction

The assembly of mechanically interlocked molecular systems about transition metal templates has been used through the years to yield catenanes, rotaxanes, knots and links.<sup>1</sup> Related architectures in which metal ions have been incorporated as an integral part of the components have also been described.<sup>2</sup> However, there are a few examples of hybrid organic–inorganic systems mechanically linked at the molecular level.<sup>3</sup>



**Fig 5.1.** Hybrid organic-inorganic [2]rotaxane **1**.

We recently described the synthesis of [2]rotaxanes comprising inorganic rings (featuring seven Cr(III) ions and one divalent metal) assembled around organic axles that contain a templating alkylammonium group separated by at least a six methylene group spacer from bulky 3,5-*t*Bu<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CO<sub>2</sub><sup>-</sup> (Fig. 5.1) or *t*BuCONH-stoppers.<sup>4</sup> These rotaxanes were obtained in different yields, influenced by the nature of the stoppers and the addition of amines or ammonium salts to the reaction mixture.

The basis of these hybrid organic–inorganic systems lies in the observation<sup>5</sup> that the formation of heterometallic wheels<sup>6</sup> of various shapes and sizes, containing seven or more trivalent Cr(III) ions and one or two divalent metal ions (typically Ni(II), Co(II), Fe(II), or Cu(II)) bridged by multiple fluoride and alkyl/aryl carboxylate anions, is templated by various organic cations, including imidazolium, N-alkylimidazolium and primary and secondary ammonium groups.<sup>5</sup> Dialkylammonium salts have previously been used to direct the assembly of rotaxanes based on crown ethers,<sup>7</sup> cucurbituril<sup>8</sup> and cyclic peptides,<sup>9</sup> so it seemed possible that they might also template the formation of rotaxanes and catenanes featuring heterometallic rings.

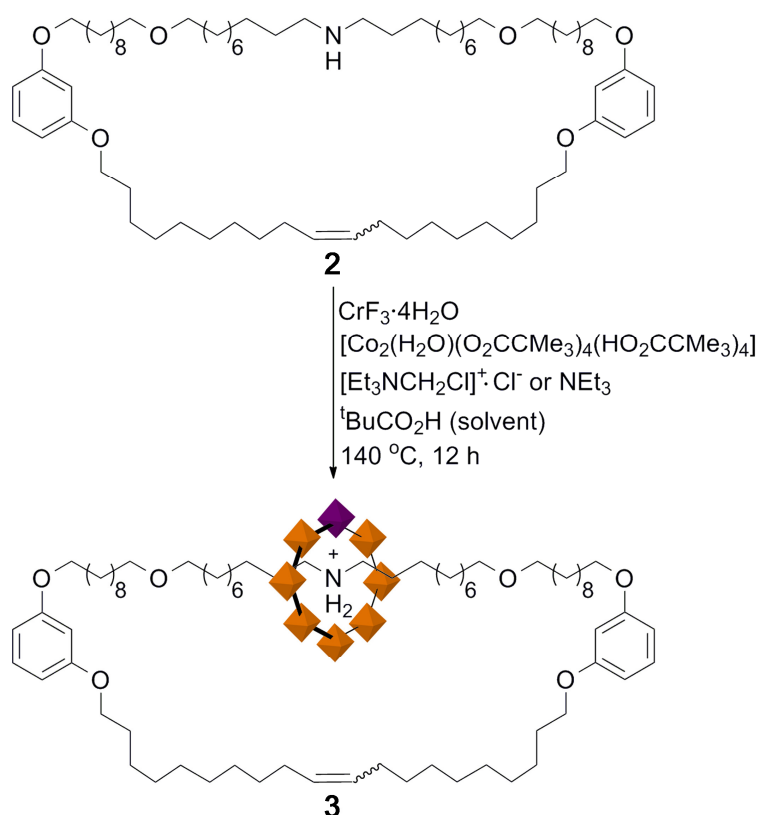
## 5.2 Results and Discussion

Here we report on the synthesis and characterization of a novel hybrid organic–inorganic [2]catenane **3** based on Co(II) as the divalent metal ion (Scheme 5.1). The seventy three-atom macrocycle **2** features a secondary amine group, prepared by ring closing metathesis from the corresponding diene (see Experimental Section). As reported<sup>4</sup>, we previously observed the need for a six methylene group spacer from the secondary amine group to the bulky 3,5-*t*-Bu<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CO<sub>2</sub><sup>-</sup> ester groups (vide supra) to overcome steric hindrance between the tert-butyl groups of the pivalates and those of the stoppers. Taking this into account, energetic calculations were performed using Spartan, to conclude that at least a fifty four member ring is needed.

The macrocycle **2** was reacted<sup>5</sup> with a 7:1 molar ratio of chromium(III) fluoride (CrF<sub>3</sub>·4H<sub>2</sub>O), a cobalt(II) metallic salt ([Co<sub>2</sub>(H<sub>2</sub>O)(*t*-BuCO<sub>2</sub>)<sub>4</sub>(*t*-BuCO<sub>2</sub>H)<sub>4</sub>], [Et<sub>3</sub>NCH<sub>2</sub>Cl]<sup>+</sup>·Cl<sup>-</sup> or NEt<sub>3</sub>, and pivalic acid as the solvent, at 140 °C for 12 h (Scheme 5.1). The corresponding [2]catenane **3** was produced in 10% yield when (chloromethyl)triethylammonium chloride was added or 39% when triethylamine was used, which is rather efficient for what is a 33 component assembly process.

In the catenane-forming reaction the octametallic ring is a monoanion (24 monoanionic ligands – 8 fluorides and 16 pivalate groups – bound to seven Cr(III)

trications and one Co(II)) whose charge is balanced by the ammonium cation formed by protonation of the thread.

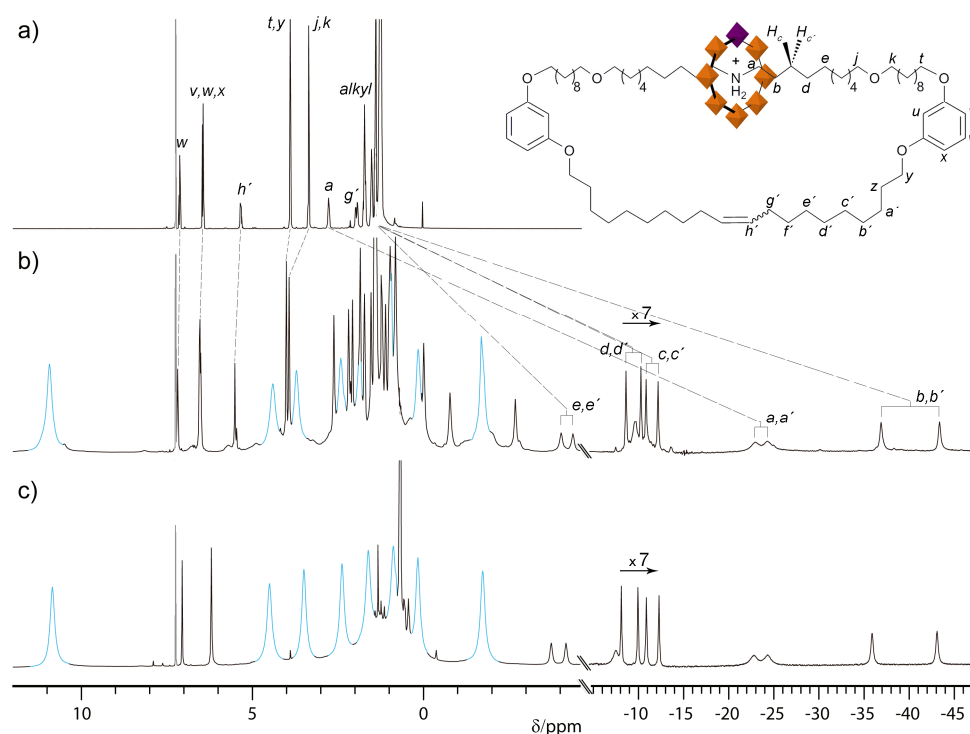


**Scheme 5.1** Synthesis of the hybrid organic-inorganic [2]catenane **3**.

Hybrid catenane **3** was characterized by analytical and spectroscopic methods. ESI mass spectrum showed an isotopic pattern in good agreement with the simulated spectrum (see Experimental section). Nuclear magnetic resonance (NMR) spectroscopy proved to be a useful technique to characterize this system. The  $^1\text{H}$  NMR spectrum of **3** (Fig. 5.2b) resembles that of the [2]rotaxane previously described (Fig. 5.2c), showing the unequal magnetic effect exerted on each geminal proton in the methylene groups of the thread due to the chirality of the ring. Two signals are observed for each pair of methylene protons, due to the two protons of each methylene group (labeled with or without a prime in Fig. 5.2) being diastereotopic (i.e., magnetically distinct) as a result of the chirality of the heterometallic ring.<sup>10</sup>



Comparison of the  $^1\text{H}$  NMR spectrum of the parent macrocycle, **2** (Fig. 5.2a), with that of the catenane, **3** (Fig. 5.2b) shows the dramatic shifts in the thread protons caused by the paramagnetic Cr(III) and Co(II) ions, the greatest shifts generally occurring for the protons closest to the heterometallic ring. The presence of one Co(II) ion among seven Cr(III) ions desymmetrizes the ring, resulting in the 16 pivalate groups being in eight magnetically nonequivalent environments (four axial and four equatorial). Slow rotation of the ring about the organic macrocycle on the NMR time scale (up to eight different C8-rotational positions of the divalent metal ion around the thread for each of the eight different types of pivalate groups) would result in many different sets of signals for the pivalate groups. However only eight resonances for pivalate groups (blue signals in Fig. 5.2b) are observed in the spectrum of **3**, consistent with rapid rotation of the ring on the NMR time scale.



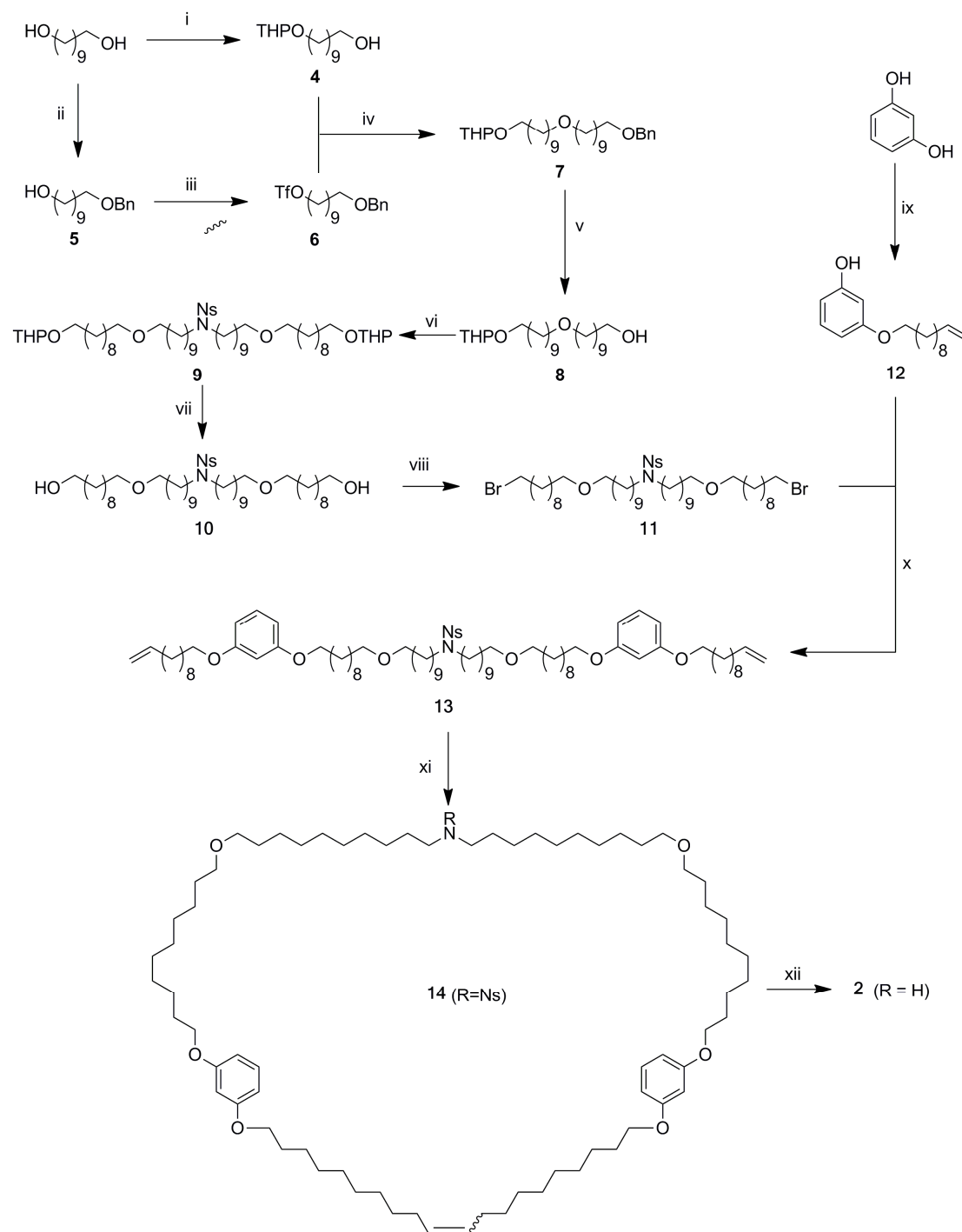
**Fig. 5.2**  $^1\text{H}$  NMR spectra (600 MHz,  $\text{CDCl}_3$ , 298 K) of (a) Macrocycle **2**; (b) [2]Catenane **3**; (c) [2]Rotaxane **1** (for comparative purposes). The eight signals shown in blue in spectra (a) and (b) are due to the 48 pivalate methyl groups of the ring. The signals below -5 ppm are shown at 7x magnification and on a compacted X-axis compared to the signals above -5 ppm. Residual solvent peaks are shown in grey.

### **5.3 Conclusions**

In conclusion, we have prepared and characterized a hybrid organic–inorganic[2]catenane through template synthesis in ~40% yield. Hybrid organic–inorganic catenanes constitute promising candidates for molecular machines that combine some of the features of the chemistry of inorganic clusters (magnetism, electronic properties) with the dynamic properties typical of organic-based interlocked molecules.

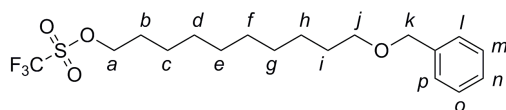
## 5.4 Experimental Section

### 5.4.1 Experimental Procedures of catenane precursors



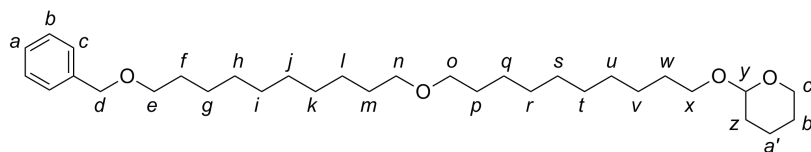
**Scheme 5.2.** Synthesis of macrocycle **2**. Reagents and conditions: (i) DHP, *p*-TsOH, THF, RT, 18h, 53%; (ii) BnCl, NaH, DMF, 0°C to RT, 18 h, 51%; (iii) Tf<sub>2</sub>O, pyridine, CH<sub>2</sub>Cl<sub>2</sub>, -20°C to RT, 2 h, 85%; (iv) 1,8-Bis(dimethylamino)naphthalene, CH<sub>2</sub>Cl<sub>2</sub>, 45°C, 78 h, 56%; (v) H<sub>2</sub>, Pd(OH)<sub>2</sub>, THF, 18h, 92%; (vi) 2-Nitrobenzene sulphonamide, DIAD, PPh<sub>3</sub>, DMAP, THF, RT, 12 h, 35%; (vii) PPTS, EtOH, 60°C, 4 h, 95%;

(viii) NBS, PPh<sub>3</sub>, THF, RT, 5 min, 93%; (ix) 11-Bromo-1-undecene, K<sub>2</sub>CO<sub>3</sub>, NaI, DMF, 80°C, 18h, 46%; (x) K<sub>2</sub>CO<sub>3</sub>, DMF, 80°C, 18h, 85%; (xi) Grubbs' first generation catalyst, toluene, RT, 24 h, 36%; (xii) mercaptoacetic acid, LiOH·H<sub>2</sub>O, DMF, RT, 12 h, 83%.



## 6

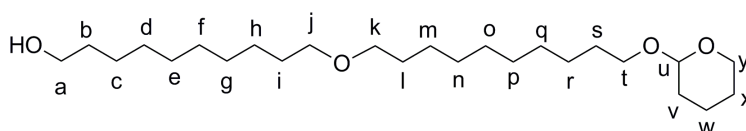
Trifluoromethanesulfonic anhydride (2.4 mL, 14.0 mmol) was added to a solution of **5** (2.7 g, 10 mmol) and pyridine (1.1 mL, 14.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) at -20°C. Formation of a white precipitate was observed immediately in the reaction mixture, which was stirred for 2 h at room temperature. After that, water (30 mL) and CH<sub>2</sub>Cl<sub>2</sub> (200 mL) were added, the organic phase extracted and washed with brine (2 × 100 mL), dried over MgSO<sub>4</sub> and concentrated under reduced pressure to give **6** as a colourless oil (3.37 g, 85%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.42-7.26 (m, 5 H, H<sub>l,m,n,o,p</sub>), 4.50-4.58 (m, 4 H, H<sub>j,k</sub>), 3.50 (t, *J* = 6.6, 2 H, H<sub>a</sub>), 0.80-1.65 (m, 16 H, H<sub>b,c,d,e,f,g,h,i</sub>). No satisfactory <sup>13</sup>C NMR was obtained and no signals due to CF<sub>3</sub> carbons were observed. Compound **6** decomposes gradually and it was used after preparation without further purification. (Prepared by Tao Long)



## 7

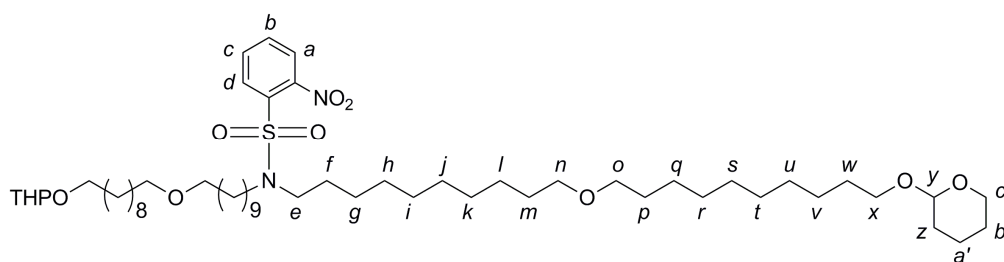
**4** (13.9, 53.8 mmol), **6** (17.8 g, 44.9 mmol) and 1,8-bis(dimethylamino)naphthalene (proton-sponge®) (9.62 g, 44.9 mmol) were mixed under nitrogen and dry CH<sub>2</sub>Cl<sub>2</sub> (600 mL) was added. The resulting mixture was refluxed under nitrogen for 78 h. The crude was washed with a saturated aqueous solution of sodium bicarbonate. The organic layer was dried (MgSO<sub>4</sub>), concentrated under reduced pressure and the

residue purified by column chromatography (40:1 hexane:AcOEt) to give **7** as a colourless oil (12.7 g, 56%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.35-7.27 (m, 5H,  $\text{H}_{a,b,c}$ ), 4.58-4.56 (m, 1H,  $\text{H}_y$ ), 4.50 (s, 2H,  $\text{H}_d$ ), 3.90-3.84 (m, 1H,  $\text{H}_{c'}$ ), 3.76-3.70 (m, 1H,  $\text{H}_{c''}$ ), 3.53-3.34 (m, 8H,  $\text{H}_{e,n,o,x}$ ), 1.89-1.78 (m, 1H,  $\text{H}_z$ ), 1.74-1.65 (m, 1H,  $\text{H}_a$ ), 1.63-1.49 (m, 12H,  $\text{H}_{f,m,p,w,z,a',b'}$ ), 1.40-1.24 (m, 24H,  $\text{H}_{g,h,i,j,k,l,q,r,s,t,u,v}$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 138.6, 130.3, 128.9, 128.7, 128.3, 127.8, 127.5, 127.4, 126.3, 125.9, 98.8, 72.8, 70.6, 70.9, 70.4, 67.6, 62.3, 30.7, 29.7, 29.5, 29.4, 26.4, 26.2, 26.1, 25.4, 19.6; LRESI-MS:  $m/z$  = 527  $[\text{M}+\text{Na}]^+$ ; HRESI-MS:  $m/z$  = 527.4079  $[\text{M}+\text{Na}]^+$  (calcd. for  $\text{C}_{32}\text{H}_{56}\text{O}_4\text{Na}$ , 527.4082  $[\text{M}+\text{Na}]^+$ ). (Prepared by Tao Long)



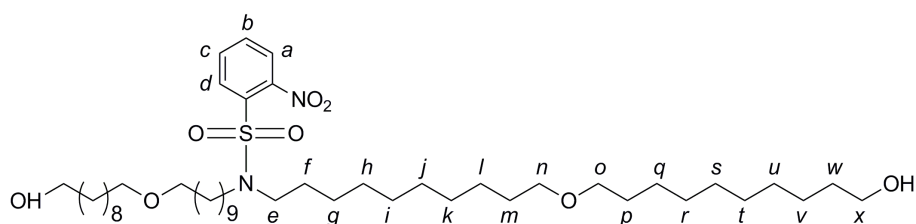
### 8

To a solution of **7** (2.10 g, 4.16 mmol) in THF (100 mL) was added  $\text{Pd}(\text{OH})_2$  (420 mg, 20 % on carbon). The suspension was repeatedly degassed and purged with  $\text{N}_2$ , then with  $\text{H}_2$  and after that stirred for 18 h at RT under  $\text{H}_2$  atmosphere. The mixture was then filtered through Celite® and the solution concentrated under reduced pressure and purified by column chromatography (4:1 hexane:EtOAc) to yield **8** as a colourless oil (1.59 g, 92%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 4.58-4.56 (m, 1H,  $\text{H}_u$ ), 3.90-3.84 (m, 1H,  $\text{H}_y$ ), 3.76-3.70 (m, 1H,  $\text{H}_y$ ), 3.64 (m, 2H,  $\text{H}_d$ ), 3.53-3.47 (m, 2H,  $\text{H}_t$ ), 3.40-3.35 (m, 4H,  $\text{H}_{j,k}$ ), 1.87-1.79 (m, 1H,  $\text{H}_v$ ), 1.75-1.9 (m, 1H,  $\text{H}_w$ ), 1.62-1.49 (m, 12H,  $\text{H}_{b,i,l,s,v,w,x}$ ), 1.35-1.23 (m, 24H,  $\text{H}_{c,d,e,f,g,h,m,n,o,p,q,r}$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 98.8, 70.9(x2), 67.7, 63.1, 62.3, 32.8, 30.8, 29.8, 29.7, 29.5(x3), 29.4, 26.2, 26.1, 25.7, 25.5, 19.7; LRESI-MS:  $m/z$  = 437  $[\text{M}+\text{Na}]^+$ ; HRESI-MS:  $m/z$  = 437.3612,  $[\text{M}+\text{Na}]^+$  (calcd. for  $\text{C}_{25}\text{H}_{50}\text{O}_4\text{Na}$ , 437.3612  $[\text{M}+\text{Na}]^+$ ).



## 9

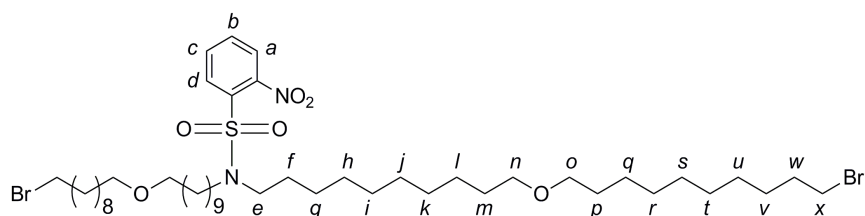
A solution of **8** (2.14 g, 5.2 mmol), 2-nitrobenzenesulfonamide (475 mg, 2.3 mmol),  $\text{PPh}_3$  (1.54 g, 5.9 mmol), DIAD (1.16 mL, 5.9 mmol) and DMAP (574 mg, 4.7 mmol) in THF (50 mL) was stirred for 18 h. The reaction mixture was then concentrated under reduced pressure and purified by column chromatography (5:1 hexane:AcOEt) to yield **9** as a colourless oil (805 mg, 35%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.02-7.98 (m, 1H,  $\text{H}_a$ ), 7.68-7.65 (m, 2H,  $\text{H}_{c,d}$ ), 7.62-7.60 (m, 1H,  $\text{H}_b$ ), 4.57- 4.55 (m, 2H,  $\text{H}_y$ ), 3.89-3.83 (m, 4H,  $\text{H}_{c'}$ ), 3.77-3.68 (m, 4H,  $\text{H}_x$ ), 3.51- 3.42 (m, 8H,  $\text{H}_{n,o}$ ), 3.26-3.23 (m, 4H,  $\text{H}_e$ ), 1.85-1.77 (m, 4H,  $\text{H}_z$ ), 1.74-1.66 (m, 4H,  $\text{H}_{a'}$ ), 1.60-1.47 (m, 16H,  $\text{H}_{m,p,v,w}$ ), 1.20-1.32 (m, 48H,  $\text{H}_{f,g,h,i,j,k,l,q,r,s,t,u}$ ).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 133.9, 133.1, 131.4, 130.7, 124.0, 98.8, 70.9(x2), 67.6, 62.3(x2), 47.1, 30.7, 29.7(x2), 29.5, 29.4, 29.4, 29.3, 29.1, 28.0, 26.6, 26.5, 26.2, 26.1, 25.5, 22.0, 21.9, 21.6, 19.6.



## 10

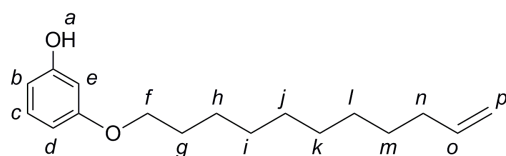
A solution of **9** (1.2 g, 1.2 mmol) and pyridinium *p*-toluenesulfonate (500 mg, 1.99 mmol) in ethanol (40 mL) was heated at 60 °C for 4 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (2:1 hexane:AcOEt) to yield **10** as a white solid (943 mg, 95%). m.p. 46-48 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.03-7.99 (m, 1H,  $\text{H}_a$ ), 7.68-7.65 (m, 2H,  $\text{H}_{c,d}$ ), 7.62-7.60 (m, 1H,  $\text{H}_b$ ), 3.64 (t,  $J$  = 6.7, 4H,  $\text{H}_x$ ), 3.40-3.37 (m, 8H,  $\text{H}_{n,o}$ ), 3.28-3.24 (m, 4H,  $\text{H}_e$ ), 1.58-1.23 (m, 64H,  $\text{H}_{f,g,h,i,j,k,l,m,p,q,r,s,t,w,u,v}$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 133.9, 133.2, 131.4,

130.7, 124.1, 71.0, 70.9, 63.1, 47.1, 32.8, 29.7, 29.5(x2), 29.4(x3), 29.2, 28.0, 26.6, 26.2, 25.7; LRAPCI-MS:  $m/z = 827 [M+H]^+$ ; HRESI-MS:  $m/z = 827.6190 [M+H]^+$  (calcd. for  $C_{46}H_{87}O_8 N_2S$ , 827.6178  $[M+H]^+$ ).



### 11

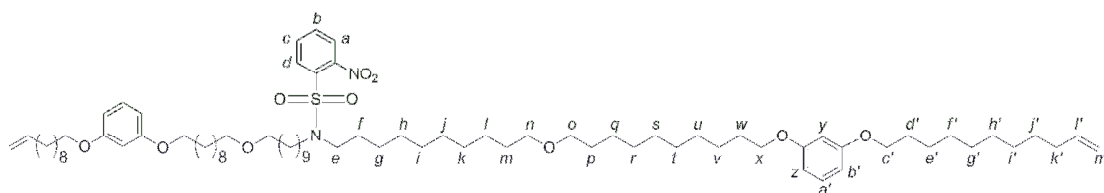
To a solution of **10** (730 mg, 0.88 mmol) and triphenylphosphine (555 mg, 2.1 mmol) in THF (20 mL) was added N-bromosuccinimide (377 mg, 2.1 mmol) and then stirred for 5 min at RT. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (2:1 hexane:AcOEt) to yield **11** as a colourless oil (781 mg, 93%).  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta = 8.02-8.00$  (m, 1H,  $H_a$ ), 7.68-7.65 (m, 2H,  $H_{c,d}$ ), 7.62-7.60 (m, 1H,  $H_b$ ), 3.42-3.37 (m, 12H,  $H_{n,o,x}$ ), 3.28-3.30 (m, 4H,  $H_e$ ), 1.88-1.81 (m, 4H,  $H_w$ ), 1.56-1.23 (m, 60H,  $H_{f,g,h,i,j,k,l,m,p,q,r,s,t,u,v}$ );  $^{13}C$  NMR (100 MHz,  $CDCl_3$ ):  $\delta = 133.9, 133.2, 131.4, 130.6, 124.1, 70.9, 47.1, 34.1, 29.8, 29.7, 29.5, 29.4, 29.3, 29.2, 28.7, 28.1, 28.0, 26.6, 26.2$ ; LRAPCI-MS:  $m/z = 951 [M+H]^+$ . HRAPCI-MS:  $m/z = 951.4524$ .  $[M+H]^+$  (calcd. for  $C_{46}H_{85}O_6N_2Br_2S$ , 951.4490  $[M+H]^+$ ).



### 12

A solution of resorcinol (11 g, 100 mmol), 11-bromo-1-undecene (11.66 g, 50 mmol), potassium carbonate (21 g, 150 mmol) and sodium iodide (1 g, 10 mmol) in DMF (300 mL) was heated at 80°C for 18 h. The reaction mixture was concentrated under reduced pressure and the residue dissolved in  $CH_2Cl_2$  (500 mL). The solution was

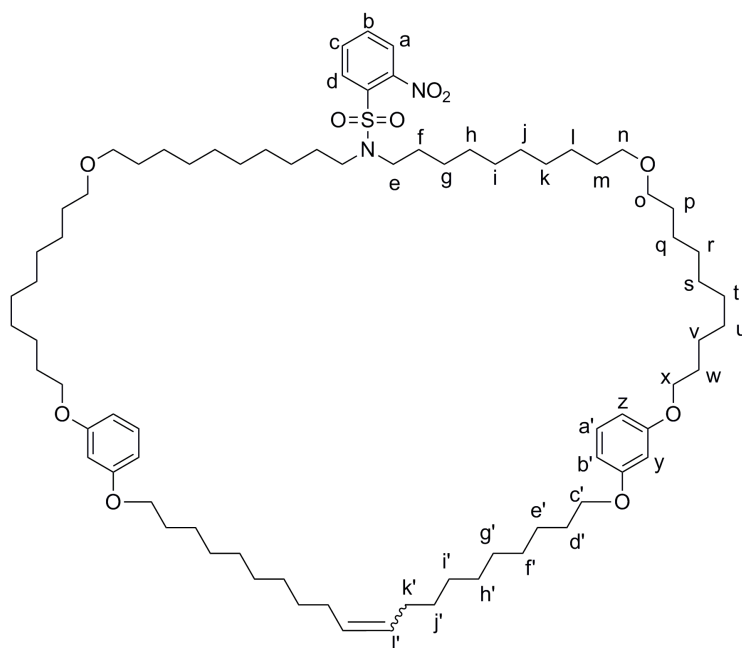
filtered through Celite® and concentrated under reduced pressure, then purified by column chromatography (10:1 hexane:AcOEt) to yield **12** as a white solid (6.03 g, 46%). m.p. 34-36°C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.12 (t,  $J$  = 8.4, 1H,  $\text{H}_c$ ), 6.51-6.48 (m, 1H,  $\text{H}_b$ ), 6.43-6.41 (m, 2H,  $\text{H}_{e,d}$ ), 5.88-5.78 (m, 1H,  $\text{H}_o$ ), 5.15 (s, 1H,  $\text{H}_a$ ), 5.04-4.93 (m, 2H,  $\text{H}_p$ ), 3.92 (t,  $J$  = 6.6, 2H,  $\text{H}_f$ ), 2.08-2.03 (m, 2H,  $\text{H}_n$ ), 1.80-1.73 (m, 2H,  $\text{H}_g$ ), 1.46-1.28 (m, 12H,  $\text{H}_{h,i,j,k,l,m}$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 160.4, 156.6, 139.2, 130.1, 114.1, 107.1, 102.0, 68.0, 33.8, 29.5, 29.4, 29.3, 29.2, 29.1, 28.9, 26.0; LRAPCI-MS:  $m/z$  = 263  $[\text{M}+\text{H}]^+$ ; HRAPCI-MS:  $m/z$  = 263.1996  $[\text{M}+\text{H}]^+$  (calcd. for  $\text{C}_{17}\text{H}_{27}\text{O}_2$ , 263.2005  $[\text{M}+\text{H}]^+$ ).



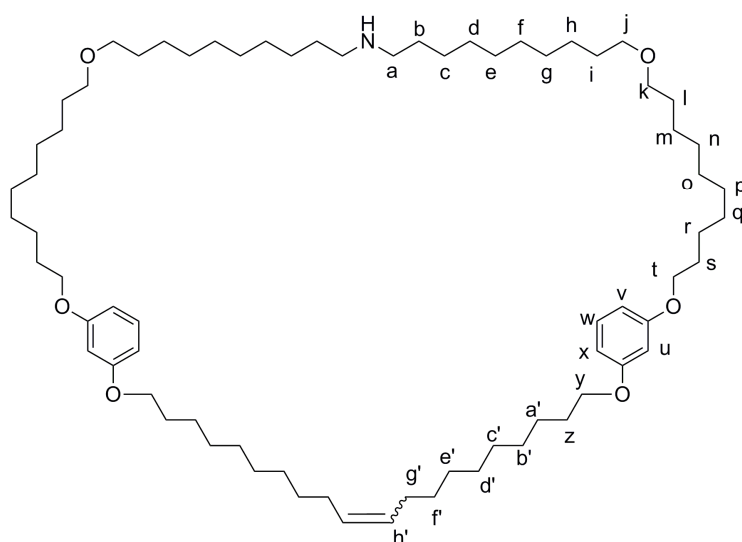
### 13

A solution of **11** (826 mg, 0.87 mmol), **12** (500 mg, 1.9 mmol) and potassium carbonate (720 mg, 5.2 mmol) in DMF (20 mL) was heated at 80°C for 18 h. The reaction mixture was concentrated under reduced pressure and the residue dissolved in  $\text{CH}_2\text{Cl}_2$  (100 mL). The solution was filtered through Celite® and concentrated under reduced pressure, then purified by column chromatography (10:1 hexane:AcOEt) to yield **13** as a yellowish solid (974 mg, 85%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.02-7.99 (m, 1H,  $\text{H}_a$ ), 7.69-7.65 (m, 2H,  $\text{H}_{c,d}$ ), 7.61-7.59 (m, 1H,  $\text{H}_b$ ), 7.14 (t,  $J$  = 8.1, 2H,  $\text{H}_{a'}$ ), 6.50-6.44 (m, 6H,  $\text{H}_{y,z,b'}$ ), 5.86-5.76 (m, 2H,  $\text{H}_{p'}$ ), 5.02-4.91 (m, 4H,  $\text{H}_{m'}$ ), 3.94-3.91 (m, 8H,  $\text{H}_{x,c'}$ ), 3.41-3.36 (m, 8H,  $\text{H}_{n,o}$ ), 3.28-3.23 (m, 4H,  $\text{H}_e$ ), 2.07-2.01 (m, 4H,  $\text{H}_{k'}$ ), 1.80-1.72 (m, 8H,  $\text{H}_{w,d'}$ ), 1.57-1.22 (m, 84H,  $\text{H}_{f,g,h,i,j,k,l,m,p,q,r,s,t,u,v,e',f',g',h',i',j'}$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 160.3, 139.2, 133.1, 131.4, 130.7, 129.7, 124.1, 114.1, 106.6, 101.3, 71.0(x2), 67.9, 47.1, 33.8, 29.8, 29.5, 29.5(x2), 29.4(x4), 29.3, 29.2, 29.1, 29.0, 28.0, 26.6, 26.2, 26.0; LRESI-MS:  $m/z$  = 1316  $[\text{M}+\text{H}]^+$ ; HRESI-MS:  $m/z$  = 1333.0116  $[\text{M}+\text{NH}_4]^+$  (calcd. for  $\text{C}_{80}\text{H}_{138}\text{N}_3\text{O}_{10}\text{S}$ , 1333.0097  $[\text{M}+\text{NH}_4]^+$ ).



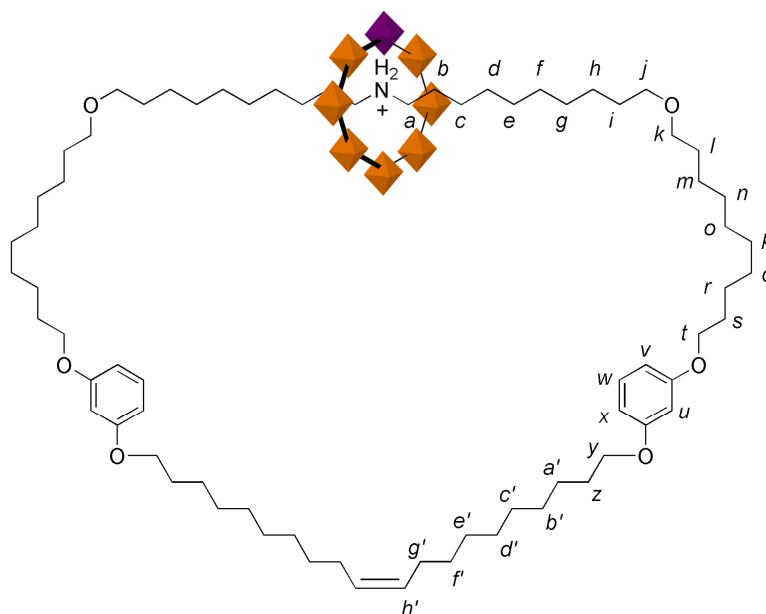
**14**

A solution of **13** (620 mg, 0.47 mmol) in dry toluene (1 L) was degassed and purged with N<sub>2</sub> for 2 h, then Grubbs' first generation catalyst was added and the solution was stirred for 24 h. After that, the reaction mixture was quenched by bubbling air for 4 h. The solution was concentrated under reduced pressure and purified by column chromatography (5:1 hexane:AcOEt) to yield **14** as a colourless oil (220 mg, 36%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 8.02-7.99 (m, 1H, H<sub>a</sub>), 7.69-7.65 (m, 2H, H<sub>c,d</sub>), 7.61-7.60 (m, 1H, H<sub>b</sub>), 7.14 (t, *J* = 8.1, 2H, H<sub>a'</sub>), 6.50-6.44 (m, 6H, H<sub>y,z,b'</sub>), 5.44-5.30 (m, 2H, H<sub>r</sub>), 3.99-3.85 (m, 8H, H<sub>x,c'</sub>), 3.45-3.34 (m, 8H, H<sub>n,o</sub>), 3.30-3.20 (m, 4H, H<sub>e</sub>), 2.07-1.92 (m, 4H, H<sub>k'</sub>), 1.83-1.70 (m, 8H, H<sub>w,d'</sub>), 1.57-1.22 (m, 84H, H<sub>f,g,h,i,j,k,l,m,p,q,r,s,t,u,v,e',f',g',h',i',j'</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 160.3, 131.4, 130.7, 130.4, 129.9, 129.7, 124.0, 106.6, 101.3, 70.9, 67.9, 47.2, 32.5, 29.7, 29.7, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 28.1, 27.1, 26.5, 26.1, 26.0; LRAPCI-MS: *m/z* = 1288 [M+H]<sup>+</sup>; HRESI-MS: *m/z* = 1304.9778 [M+NH<sub>4</sub>]<sup>+</sup> (calcd. for C<sub>78</sub>H<sub>134</sub>O<sub>10</sub>N<sub>3</sub>S, 1304.9784 [M+NH<sub>4</sub>]<sup>+</sup>).



## 2

A solution of **14** (180 mg, 0.14 mmol), mercaptoacetic acid (64 mg, 0.70 mmol), and LiOH·H<sub>2</sub>O (59 mg, 1.4 mmol) in DMF (10 mL) was stirred at RT for 12 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in AcOEt (50 mL), washed with brine (2 × 20 mL). The organic layer was concentrated under reduced pressure and purified by column chromatography (50:1 CH<sub>2</sub>Cl<sub>2</sub>:CH<sub>3</sub>OH) to yield **2** as a colourless oil (132 mg, 83%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.14 (t, *J* = 8.1, 2H, H<sub>w</sub>), 6.52-6.40 (m, 6H, H<sub>u,v,x</sub>), 5.44-5.33 (m, 2H, H<sub>h'</sub>), 3.98-3.89 (m, 8H<sub>t,y</sub>), 3.45-3.36 (m, 8H, H<sub>j,k</sub>), 2.92-2.76 (m, 4H, H<sub>a</sub>), 2.09-1.93 (m, 4H, H<sub>g'</sub>), 1.84-1.67 (m, 8H, H<sub>s,z</sub>), 1.63-1.07 (m, 84H, H<sub>b,c,d,e,f,g,h,i,l,m,n,o,p,q,r,a',b',c',d',e',f'</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 160.3, 131.4, 130.7, 130.4, 129.9, 129.7, 124.0, 106.6, 101.3, 70.9, 67.9, 47.2, 32.5, 29.7, 29.7, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 28.1, 27.1, 26.5, 26.1, 26.0; LRAPCI-MS: *m/z* = 1103 [M+H]<sup>+</sup>; HRESI-MS: *m/z* = 1102.9729 [M+H]<sup>+</sup> (calcd. for C<sub>72</sub>H<sub>128</sub>O<sub>6</sub>N, 1102.9736).

**3**

**2** (39 mg, 35  $\mu\text{mol}$ ), pivalic acid (144 mg, 1.4 mmol) and triethylamine (3.6 mg, 35  $\mu\text{mol}$ ) were stirred at 140  $^{\circ}\text{C}$  for 15 min in a Teflon flask under  $\text{N}_2$  atmosphere. Then,  $\text{CrF}_3 \cdot 4\text{H}_2\text{O}$  (32 mg, 17.7 mmol) and  $[\text{Co}(\text{OH}_2)(\text{O}_2\text{CCMe}_3)_4(\text{HO}_2\text{CCMe}_3)_4]$  (17 mg, 17  $\mu\text{mol}$ ) were added, and the solution was stirred at 140  $^{\circ}\text{C}$  for 12 h. After that, the reaction mixture was cooled to RT and  $\text{CH}_3\text{CN}$  (20 mL) was added. The green precipitate was filtered, washed with  $\text{CH}_3\text{CN}$ , dissolved in  $\text{Et}_2\text{O}$ , concentrated under reduced pressure and purified by column chromatography (100:2 hexane:AcOEt then 100:6 hexane:AcOEt) to yield **3** (32 mg, 39%).  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 10.93 (br s, 18H,  $\text{H}_{\text{pivalate}}$ ), 7.24-7.14 (m, 2H,  $\text{H}_w$ ), 6.60-6.47 (m, 6H,  $\text{H}_{u,v,x}$ ), 5.59-5.44 (m, 2H,  $\text{H}_{h'}$ ), 4.43 (br s, 18H,  $\text{H}_{\text{pivalate}}$ ), 4.12-3.99 (m, 8H,  $\text{H}_{t,y}$ ), 3.96-3.89 (br m, 8H,  $\text{H}_{j,k}$ ), 3.74 (br s, 18H,  $\text{H}_{\text{pivalate}}$ ), 2.96-(-0.34) (br m, 134H,  $\text{H}_{\text{alkyl,pivalate}}$ ), 0.19 (br s, 18H,  $\text{H}_{\text{pivalate}}$ ), 0.03 (br s, 18H,  $\text{H}_{\text{pivalate}}$ ), -1.65 (br s, 18H,  $\text{H}_{\text{pivalate}}$ ), -3.97 (s, 2H,  $\text{H}_e$ ), -4.31 (s, 2H,  $\text{H}_e$ ), -8.58 (s, 2H,  $\text{H}_d$ ), -10.23 (s, 2H,  $\text{H}_d$ ), -10.81 (s, 2H,  $\text{H}_c$ ), -12.11 (s, 2H,  $\text{H}_c$ ), -22.91 (s, 2H,  $\text{H}_a$ ) - 24.20 (s, 2H,  $\text{H}_a$ ), -36.80 (s, 2H,  $\text{H}_b$ ), -43.27 (s, 2H,  $\text{H}_b$ ). LRESI-MS:  $m/z$  = 3296  $[\text{M}+\text{H}]^+$ , 3318  $[\text{M}+\text{Na}]^+$  (Prepared by Dr. David Schultz)

## 5.4.2. Fragmentation Data of Compound 3

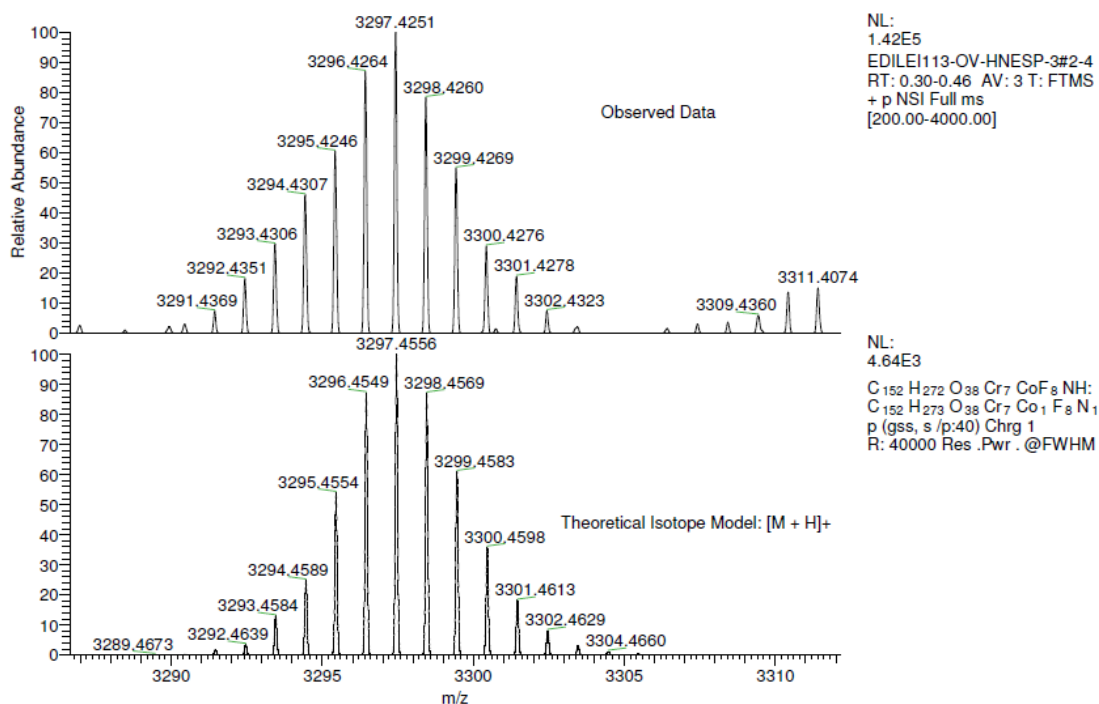


Figure 5.3. the isotopic distribution of the molecular ion and the corresponding simulated pattern

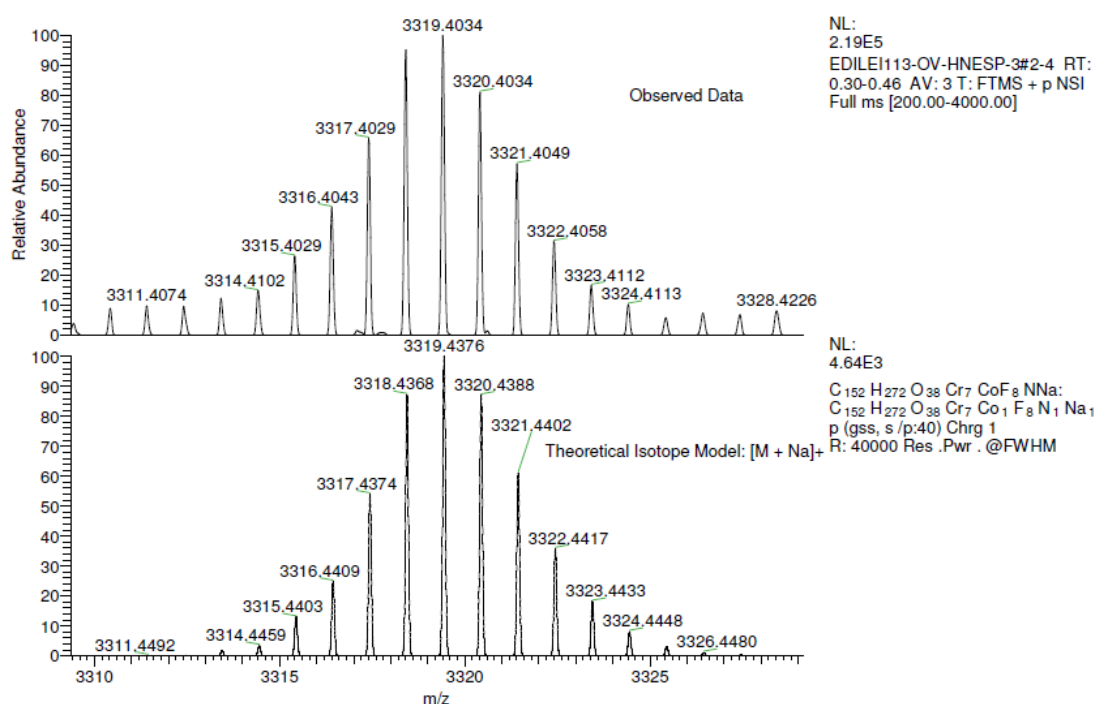


Figure 5.4. the isotopic distribution of the molecular ion plus sodium and the corresponding simulated pattern.

## 5.5 References

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# Appendix

## Published Papers

*“Active Metal Template Synthesis of [2]Catenanes.”* Stephen M. Goldup, David A. Leigh, Tao. Long, Paul R. McGonigal, Mark. D. Symes and Jhenyi Wu, *J. Am. Chem. Soc.* **2009**, 131, 15924–15929.

*“En Route to a Molecular Sheaf: Active Metal Template Synthesis of a [3]Rotaxane With Two Axles Threaded Through One Ring.”* Hei Man Cheng, David A. Leigh, Francesca Maffei, Paul R. McGonigal, Alexandra M. Z. Slawin and Jhenyi Wu. *J Am Chem Soc*, **2011**, 133, 12298-12303.

*“Active Metal Template Synthesis of a Molecular Trefoil Knot.”* Perdita E. Barran, Harriet L. Cole, Stephen M. Goldup, David A. Leigh, Paul R. McGonigal, Mark D. Symes, Jhenyi Wu and Michael Zengerle. *Angew. Chem. Int. Ed.* **2011**, 50, 12280-12284.

Back cover picture: *“Active Metal Template Synthesis of a Molecular Trefoil Knot.”* Perdita E. Barran, Harriet L. Cole, Stephen M. Goldup, David A. Leigh, Paul R. McGonigal, Mark D. Symes, Jhenyi Wu and Michael Zengerle. *Angew. Chem. Int. Ed.* **2011**, 50, 12366.

### Active Metal Template Synthesis of [2]Catenanes

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**Abstract:** The synthesis of [2]catenanes by single macrocyclization and double macrocyclization strategies using Cu(I) ions to catalyze covalent bond formation while simultaneously acting as the template for the mechanically interlocked structure is reported. These “active metal template” strategies employ appropriately functionalized pyridine ether or bipyridine ligands and either the CuAAC “click” reaction of azides with terminal alkynes or the Cu(I)-mediated Cadiot–Chodkiewicz heterocoupling of an alkyne halide with a terminal alkyne. Using one macrocyclic and one acyclic building block, heterocircuit (the rings are constitutionally different) [2]catenanes are produced via the single macrocyclization route in up to 53% yield by optimizing the reaction conditions and relative stoichiometry of the starting materials. Alternatively, with the active template CuAAC reaction, a single acyclic unit can be used to form a homocircuit (two identical rings) [2]catenane in 46% yield through a one-pot, double macrocyclization, procedure. Remarkably, <7% of the corresponding noninterlocked macrocycle is isolated from this reaction, indicating the efficacy of Cu(I) as both a template for the catenane and a catalyst for covalent bond formation in the reaction.

#### Introduction

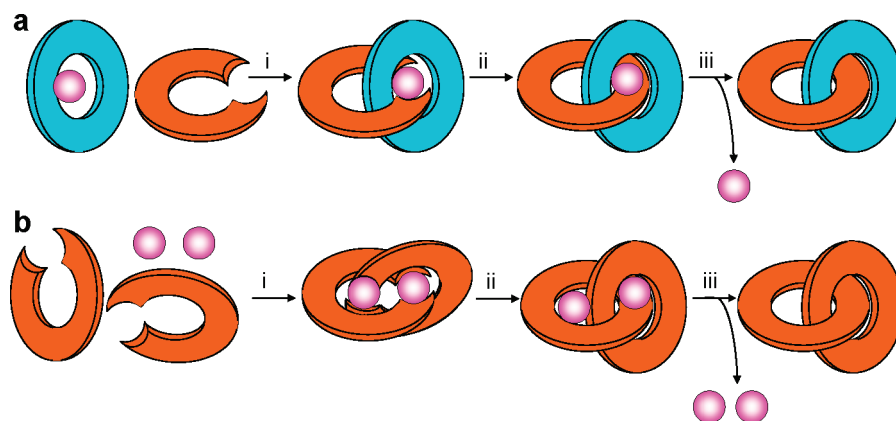
The synthesis of catenanes and rotaxanes was revolutionized by the application of template-directed syntheses,<sup>1</sup> in which the components are preorganized prior to covalent capture of the interlocked architecture. Although a large number of different types of template-directed reactions have been successfully employed to form rotaxanes in threading-followed-by-stoppering

strategies,<sup>1a</sup> “clipping” approaches to rotaxanes and catenanes (involving single or double macrocyclization of ligands, directed by the template)<sup>2</sup> are rather more demanding and have only been demonstrated with a small number of different macrocyclization reaction types. Of these, Williamson ether synthesis,<sup>2</sup> the Huisgen–Meldal–Fokin Cu(I)-catalyzed 1,3-cycloaddition of azides with terminal alkynes (the CuAAC “click” reaction),<sup>3,4</sup> amide or ester bond-forming reactions,<sup>5</sup> ring-closing metathesis,<sup>6</sup> imine bond formation,<sup>1u,6f,7</sup> and metal–ligand coordination<sup>8</sup> are the most commonly used. The effectiveness of these reactions for catenane synthesis lies in their reactive end groups being sufficiently stable in solution to react overwhelmingly in the desired fashion even when accessing the required reaction geometry is a rare event (as it is for the cyclization of large

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**Figure 1.** The active metal template approach to catenane synthesis. (a) Single macrocyclization route: (i) Template assembly of a macrocyclic ligand and an acyclic ligand about the metal ion (shown in pink) is followed (ii) by a covalent bond-forming reaction between the end groups of the acyclic ligand, catalyzed by the metal ion, through the cavity of the macrocycle. (iii) Decomplexation affords the metal-free [2]catenane. (b) Double macrocyclization route: (i) Template assembly of the acyclic ligands about one or more metal ions is followed by (ii) successive or simultaneous macrocyclization reactions. (iii) Decomplexation affords the metal-free homocircuit (both macrocycles are the same) [2]catenane. The two routes are analogous to the single and double macrocyclization strategies introduced by Sauvage for the synthesis of catenanes by “passive” metal template methods.<sup>2</sup>

rings), and hence give predominantly macrocyclic products under high dilution. The yield of catenane versus noninterlocked macrocycle then depends on how effectively the template preorganizes the ring-closing reaction to take place while one component is threaded through the cavity of the other.

We recently developed<sup>9</sup> an approach to rotaxane synthesis in which a metal ion ligated endotopically within a macrocycle mediates bond formation between two suitably functionalized building blocks through the macrocycle cavity to assemble the

thread. This “active metal template” strategy<sup>9</sup> takes inspiration from ligand couplings employed in transition metal catalysis and opens up a broad range of metal-mediated bond formations for possible use in the synthesis of rotaxanes, the requirement being that the key bond-forming reaction can be directed by the catalyst to proceed through the macrocyclic cavity rather than external to it. Such active metal template processes, where a single species acts as both the template and the catalyst for covalent bond formation, clearly also offer potential for the synthesis of catenanes (Figure 1). Using a metal ion to simultaneously bind to and activate the tethered ends of an acyclic building block to react through the cavity of a macrocycle could lead to reactions with unstable intermediates that would otherwise not lead to interlocked products being used for possible catenane-forming reactions. Active template processes also offer the possibility of traceless assembly<sup>9i</sup> (as the coordinating functional groups are often chemically changed during the reaction into noncoordinating elements) and could be used to prepare catenanes containing multiple rings or having only very weak residual intercomponent interactions, molecules

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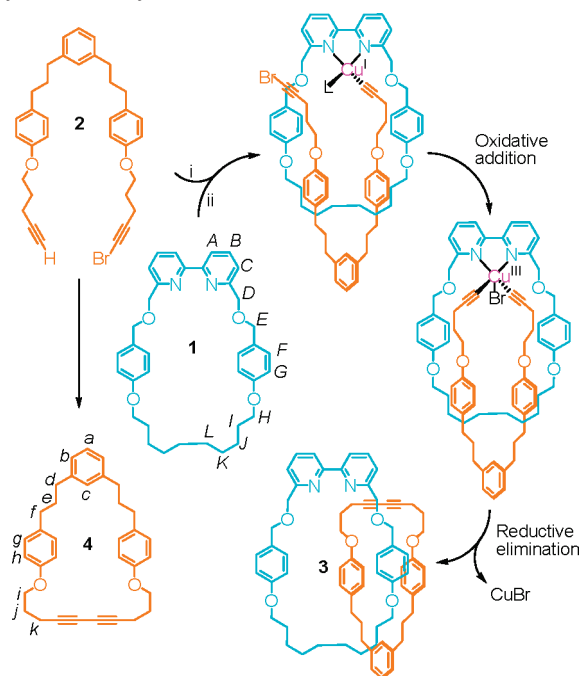
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that are often difficult or impossible to achieve with standard template-directed approaches. Here, we report on the application of the active metal template concept to catenane synthesis using both single macrocyclization and double macrocyclization strategies. Heterocircuit (the rings are different) and homocircuit (the rings are the same) [2]catenanes are assembled using appropriately functionalized bidentate pyridine ether or bipyridine ligands and either the Cu(I)-catalyzed CuAAC reaction or the Cu(I)-mediated Cadiot–Chodkiewicz<sup>10</sup> heterocoupling of an alkynyl halide and a terminal alkyne.

### Active Metal Template [2]Catenane Synthesis Using the Cadiot–Chodkiewicz Reaction

We initially investigated a modified Cadiot–Chodkiewicz coupling<sup>11</sup> of a bromoalkyne with a terminal alkyne mediated by a Cu<sup>I</sup> complex of bidentate bipyridyl macrocycle **1**,<sup>9d</sup> due to its efficacy in active template rotaxane-forming reactions.<sup>9g</sup>

**Scheme 1.** Active Metal Template Cadiot–Chodkiewicz Synthesis of [2]Catenane **3** from Bipyridyl Macrocycle **1** and Alkyne-Bromoalkyne **2**<sup>a</sup>

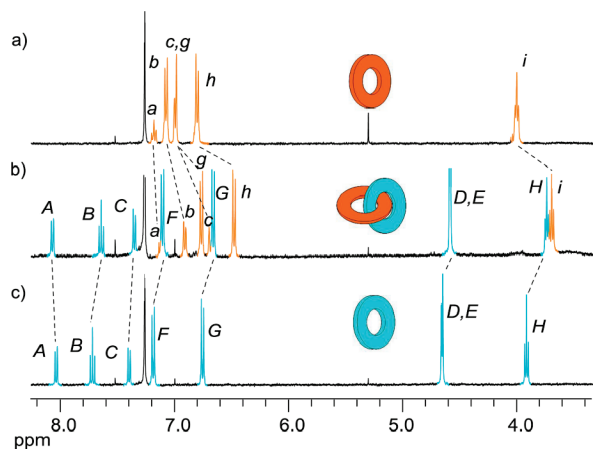


<sup>a</sup> Reagents and conditions: (i) LiHMDS, THF,  $-78^{\circ}\text{C}$ ; (ii) CuI (1 equiv), 5 equiv of **2**,  $80^{\circ}\text{C}$ , 72 h, 21% (over two steps). L = I, Br, or THF.

Acyclic unit **2** has no potential metal-coordinating sites other than the terminal alkyne and bromoalkyne reactive functional groups and should cyclize to form a ring of similar size and shape to others previously demonstrated to accommodate thread-forming reactions in active template rotaxane syntheses.<sup>9</sup> Building block **2** was treated with LiHMDS ( $\text{LiN}(\text{SiMe}_3)_2$ ) at  $-78^{\circ}\text{C}$  and then added to a solution of macrocycle **1** and CuI in THF, and the resulting mixture was stirred for 4 days at room temperature (Scheme 1), a procedure similar to that used successfully<sup>9g</sup> for rotaxane formation. However, little of the desired catenane product (**3**) was observed, and only a small amount of **2** was consumed under these conditions. Increasing the reaction concentration, raising the reaction temperature to  $80^{\circ}\text{C}$ , and employing a 5-fold excess of **2** ultimately gave [2]catenane **3** in 21% yield. The proposed mechanism for the active metal template Cadiot–Chodkiewicz catenane synthesis is shown in Scheme 1.<sup>12</sup> The modest yield illustrates how the catenane-forming reaction, in which the reactive end groups must be tethered together, is much more demanding in terms of conformational requirements of the ligands, and probably steric effects, than the equivalent rotaxane-forming reaction (for which nontethered functional groups are reacted through the macrocycle cavity to form the interlocked thread). The yield of

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**Figure 2.** Partial  $^1\text{H}$  NMR spectra (400 MHz,  $\text{CDCl}_3$ , 300 K) of (a) bisacetylene macrocycle **4**, (b) [2]catenane **3**, and (c) bipyridine macrocycle **1**. The assignments correspond to the lettering shown in Scheme 1.

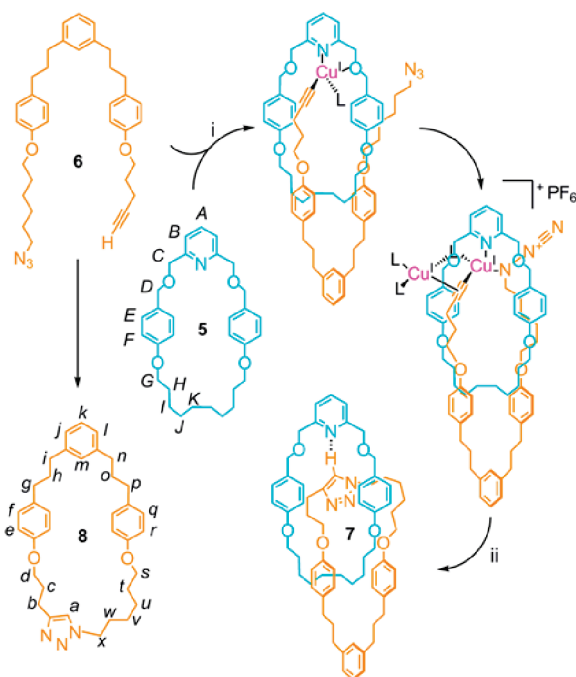
catenane also suffers because the bromoalkyne moiety is present during treatment of the terminal alkyne of **2** with LiHMDS, prior to transmetalation with copper. This leads to some decomposition of the alkyne halide, whereas in the corresponding rotaxane-forming reactions, the terminal alkyne could be treated with LiHMDS and transmetalated with copper before the alkyne halide was added to the reaction mixture.

As a heterocircuit catenane (the two rings are different), the interlocked nature of **3** was apparent from both mass spectrometry ( $m/z$  of the molecular ion) and  $^1\text{H}$  NMR spectroscopy. The  $^1\text{H}$  NMR spectrum of [2]catenane **3** in  $\text{CDCl}_3$  (Figure 2b) displays upfield shifts of nearly all of the signals with respect to those of the noninterlocked components (Figure 2a and c). Such shielding is typical of interlocked architectures in which the aromatic rings of one component are face-on to another component and is most conspicuous for  $\text{H}_\text{F}$ ,  $\text{H}_\text{G}$ , and  $\text{H}_\text{H}$  of macrocycle **1** and  $\text{H}_\text{C}$ ,  $\text{H}_\text{h}$ , and  $\text{H}_\text{i}$  of macrocycle **4**. The ubiquity of the upfield shifts implies that the two rings are largely free to rotate with respect to one another, as might be expected in a system where there are no strong intercomponent interactions to stabilize a particular coconformation.

### Active Metal Template [2]Catenane Synthesis Using the CuAAC “Click” Reaction: Single Macrocyclization Strategy

The qualified success of the catenane-forming active template Cadiot–Chodkiewicz reaction prompted us to try using the CuAAC “click” reaction to form [2]catenanes (Scheme 2, Table 1), a reaction that had also been previously successfully applied to the active template synthesis of rotaxanes<sup>9a,d</sup> and passive template syntheses of both rotaxanes<sup>11,13</sup> and catenanes.<sup>4</sup> When

**Scheme 2.** Single Macrocyclization Strategy Active Metal Template CuAAC Synthesis of [2]Catenane **7** from Pyridyl Macrocycle **5** and Azide–Alkyne **6**<sup>a</sup>



<sup>a</sup> Reagents and conditions: (i)  $[\text{Cu}(\text{CH}_3\text{CN})_4](\text{PF}_6)$ ,  $\text{CH}_2\text{Cl}_2$ , or  $\text{C}_2\text{H}_4\text{Cl}_2$ ; (ii) EDTA,  $\text{NH}_3(\text{aq})$ .  $\text{L} = \text{CH}_3\text{CN}$ , alkyne, azide, or donor atom from another molecule. For the effect of conditions and reagent stoichiometry on the reaction yield, see Table 1.

**Table 1.** Influence of Reaction Conditions and Reagent Stoichiometry on the Single Macrocyclization Strategy Active Metal Template CuAAC Synthesis of [2]Catenanes **7** and **9** (Schemes 2 and 3)<sup>a</sup>

entry	macrocycle (concentration)	equiv of <b>6</b>	$T/^\circ\text{C}$	time/h	conversion to triazole products (%)	yield (%) of [2]catenane <b>5</b> → <b>7</b>
1 <sup>a</sup>	<b>5</b> (6.5 mM)	1	RT	24	15 <sup>b</sup>	<5 <sup>b</sup>
2	<b>5</b> (6.5 mM)	1	80	96	90	16
3	<b>5</b> (6.5 mM)	5	80	240	>98	25
4	<b>5</b> (1.25 mM)	5	80	288	>98	53
5	<b>1</b> (1 mM)	5	80	500	50	50
6	<b>1</b> (5 mM)	5	80	170	>98	49

<sup>a</sup> One equivalent of  $[\text{Cu}(\text{CH}_3\text{CN})_4](\text{PF}_6)$  was used relative to the macrocycle (**1** or **5**). All reactions were carried out in  $\text{C}_2\text{H}_4\text{Cl}_2$ , except entry 1 ( $\text{CH}_2\text{Cl}_2$ ). <sup>b</sup> Yield estimated by  $^1\text{H}$  NMR.

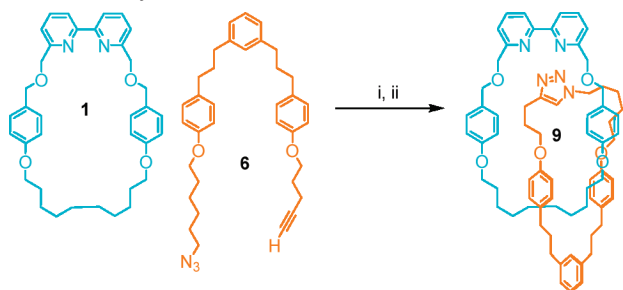
an equimolar mixture of macrocycle **5**,<sup>14</sup>  $[\text{Cu}(\text{CH}_3\text{CN})_4](\text{PF}_6)$ , and the acyclic azide–alkyne unit **6** in dichloromethane was stirred for 24 h at room temperature, a low conversion to triazole products was observed with only trace amounts of catenane apparent in the  $^1\text{H}$  NMR analysis of the crude reaction mixture (Table 1, entry 1). Changing the solvent to 1,2-dichloroethane and raising the temperature to 80  $^\circ\text{C}$  afforded [2]catenane **7** in 16% yield with near complete conversion of **6** to triazole products (Table 1, entry 2). Finally, by increasing the number of equivalents of **6** relative to **5** and running the reaction at greater dilution (which required extended reaction times), the yield of catenane **7** was increased to a pleasing 53% (Table 1, entry 4). Isolation of the metal-free catenane was facilitated by washing the crude product mixture with a basic EDTA solution.

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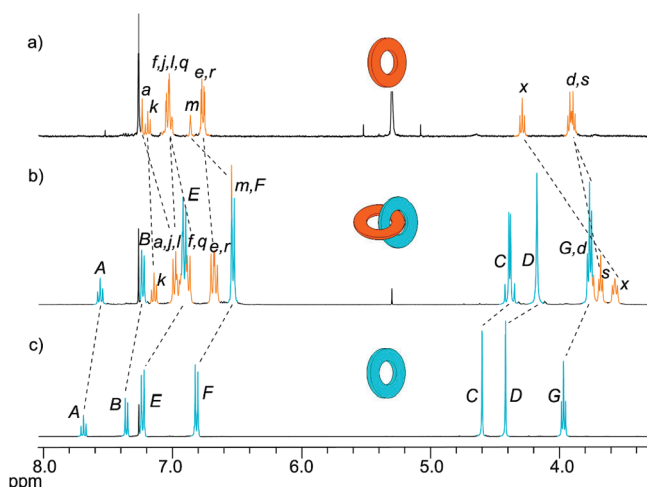
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**Scheme 3.** Single Macrocyclization Strategy Active Metal Template CuAAC Synthesis of [2]Catenane **9** from Bipyridyl Macrocycle **1** and Azide-Alkyne **6**<sup>a</sup>



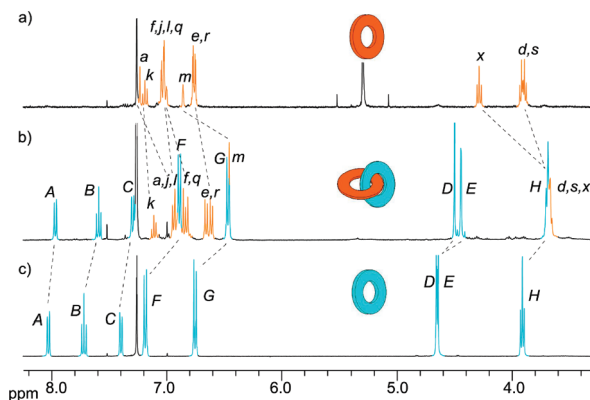
<sup>a</sup> Reagents and conditions: (i)  $[\text{Cu}(\text{CH}_3\text{CN})_4](\text{PF}_6)_3$ ,  $\text{C}_2\text{H}_4\text{Cl}_2$ , 80 °C, 7–21 d. (ii) EDTA,  $\text{NH}_3(\text{aq})$ , 49–50% (over two steps). For the effect of concentration on the time of reaction, see Table 1.



**Figure 3.** Partial  $^1\text{H}$  NMR spectra (400 MHz,  $\text{CDCl}_3$ , 300 K) of (a) triazole macrocycle **8**, (b) [2]catenane **7**, and (c) pyridine macrocycle **5**. The assignments correspond to the lettering shown in Scheme 2.

The  $^1\text{H}$  NMR spectrum of catenane **7** (Figure 3b) shows significant upfield shifts of various signals ( $\text{H}_x \sim 0.6$  ppm,  $\text{H}_m \sim 0.4$  ppm,  $\text{H}_E \sim 0.3$  ppm, and  $\text{H}_F \sim 0.3$  ppm) with respect to the components (Figure 3a and c), consistent with its interlocked architecture. Interestingly, signals corresponding to  $\text{H}_C$  appear as an AB system, indicating that the two faces of the pyridyl macrocycle are inequivalent. This is a result of the triazole group making the ring threaded through the pyridyl macrocycle inherently unsymmetrical. The chemical shift of  $\text{H}_a$  of the triazole group suggests it may form a  $\text{C}-\text{H}\cdots\text{N}$  hydrogen bond<sup>15</sup> with the pyridine nitrogen atom of the other macrocycle.

Both pyridyl and bipyridyl macrocycles have been found to undergo efficient active template rotaxane assembly with the CuAAC reaction,<sup>9d</sup> although the kinetics of the reactions are very different (the bipyridyl macrocycle reaction is considerably slower) as a result of the reactions proceeding through different types of intermediates. The same trend was seen with the active template catenane-forming reaction (Scheme 3 and Table 1, entries 5 and 6). Although good yields (49–50%) of [2]catenane **9** could be obtained, they required long reaction times (7–21 days) at 80 °C and/or higher reaction concentrations. It is testimony to the very specific reaction preferences of the azide and alkyne functional groups under Cu(I) catalysis that they survive for so long without undergoing side reactions until the



**Figure 4.** Partial  $^1\text{H}$  NMR spectra (400 MHz,  $\text{CDCl}_3$ , 300 K) of (a) triazole macrocycle **8**, (b) [2]catenane **9**, and (c) bipyridine macrocycle **1**. The assignments correspond to the lettering indicated for macrocycles **1** and **8** in Schemes 1 and 2, respectively.

apparently very rare event of the groups being in just the right position to react to form catenane occurs.

The  $^1\text{H}$  NMR spectrum of catenane **9** (Figure 4b) again shows upfield shifts of most of its signals with respect to its noninterlocked components (Figure 4a and c). Signals  $\text{H}_F$  and  $\text{H}_G$  of bipyridine macrocycle **1** are each shifted by  $\sim 0.2$  ppm, consistent with  $\pi-\pi$  stacking between the aromatic rings to which  $\text{H}_F$  and  $\text{H}_G$  are attached and the aromatic rings of macrocycle **8**. As in catenane **7**, the signals corresponding to  $\text{H}_E$  appear as an AB system, although this is less pronounced than in the pyridine macrocycle-derived catenane.

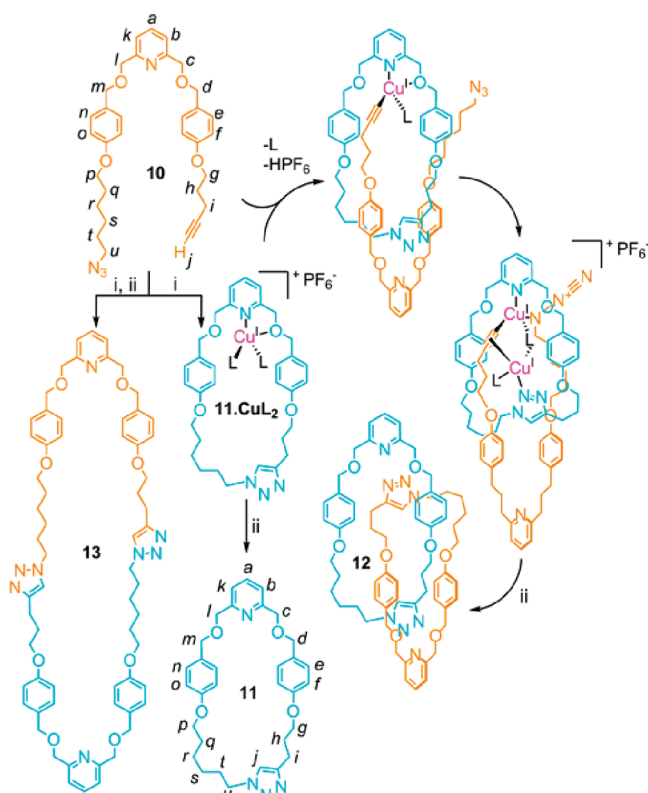
### Active Metal Template [2]Catenane Synthesis Using the CuAAC “Click” Reaction: Double Macrocyclization of Two Identical Acyclic Building Blocks

The active template reactions investigated so far (Schemes 1–3) featured a preformed macrocycle as one of the components and involved a single macrocyclization step (Figure 1a) leading to heterocircuit catenanes. We were interested to see whether it would be possible to extend this concept to an active template double macrocyclization strategy (Figure 1b) in which a homocircuit (both interlocked rings constitutionally identical) [2]catenane was assembled in one pot by two successive macrocyclization reactions (the final one, at least, having to be templated by the catalyst) of a single type of building block (Scheme 4).

Ligand **10** incorporates the terminal alkyne and azide groups necessary for the CuAAC reaction, together with a pyridine group for coordination to a Cu ion catalyzing the ring closure of another molecule of **10**. The covalent framework of the ligand was chosen to mimic macrocycle **5** and acyclic unit **6**, which combine effectively to give catenane in the single macrocyclization active template CuAAC reaction (Scheme 2).

Building block **10** was dissolved in  $\text{C}_2\text{H}_4\text{Cl}_2$  with one-half of an equivalent of  $[\text{Cu}(\text{CH}_3\text{CN})_4](\text{PF}_6)_3$ , and the solution was heated at 80 °C for 5 days (Scheme 4). The yield of [2]catenane proved to be highly dependent on the reaction concentration (Table 2), presumably a reflection of the delicate balance between various types of coordination complexes that can give rise to oligomers, noninterlocked macrocycles, or catenane. Carrying out the reaction at an initial 0.3 mM concentration of **10** gave a remarkable 46% yield of metal-free [2]catenane **12**, isolated after workup with a basic EDTA solution and purification by column chromatography. Very little (<7% as compared

(15) Li, Y.; Flood, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 12111–12122.

**Scheme 4.** Double Macrocyclization Strategy Active Metal Template CuAAC Synthesis of [2]Catenane **12** from Azide–Alkyne **10**<sup>a</sup>

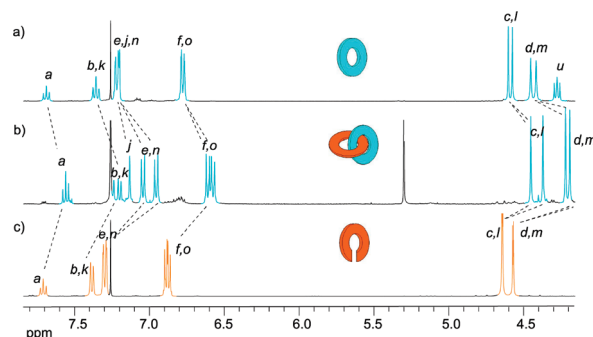
<sup>a</sup> Reagents and conditions: (i)  $[\text{Cu}(\text{CH}_3\text{CN})_4](\text{PF}_6)$ ,  $\text{C}_2\text{H}_4\text{Cl}_2$ , 80 °C, 5 d. (ii) EDTA,  $\text{NH}_3(\text{aq})$ . L =  $\text{CH}_3\text{CN}$ , alkyne, azide, or donor atom from another molecule. For the effect of concentration on catenane yield, see Table 2.

**Table 2.** Influence of Concentration on the Double Macrocyclization Strategy Active Metal Template CuAAC Synthesis of [2]Catenane **12** (Scheme 4)<sup>a</sup>

entry	[ <b>10</b> ] (mM)	conversion to triazole products (%)	ratio catenane <b>12</b> :macrocycles <b>11</b> and <b>13</b>	yield of [2]catenane <b>10</b> → <b>12</b> (%)
1	15	>98	2:3	8
2	6	>98	2:3	16
3	3	>98	5:2	25
4	1	>98	3:1	30
5	0.3	>98	7:1	46
6	0.08	65	1:1	40
7	0.03	25	1:6	6

<sup>a</sup> One-half of an equivalent of  $[\text{Cu}(\text{CH}_3\text{CN})_4](\text{PF}_6)$  was used relative to **10**. All reactions were performed in  $\text{C}_2\text{H}_4\text{Cl}_2$  at 80 °C over 120 h.

to 46% [2]catenane) of noninterlocked macrocycles **11** and **13** were isolated from the reaction reported in Table 2, entry 5. It is intriguing that even at these relatively low concentrations the double macrocyclization reaction is more selective for the [2]catenane than the corresponding single macrocyclization employing pyridine macrocycle **5** and 1 equiv of the acyclic azide–alkyne building block **6** (Scheme 2 and Table 1, entry 2). A possible explanation could be that the second Cu(I) ion involved in the mechanism of these reactions<sup>3,9d</sup> becomes coordinated to the triazole nitrogen of macrocycle **11**, resulting

**Figure 5.** Partial <sup>1</sup>H NMR spectra (400 MHz,  $\text{CDCl}_3$ , 300 K) of (a) macrocycle **11**, (b) [2]catenane **12**, and (c) azide–alkyne building block **10**. The assignments correspond to the lettering shown in Scheme 4.

in a reaction geometry in which interlocking is significantly enhanced, as shown in Scheme 4. As the two Cu(I) centers are linked via both a bridging ligand, L, and coordination to the alkyne, the azide is forced to approach the reactive center through the cavity of macrocycle **11** for the CuAAC reaction to occur, leading predominantly to catenane.

The structure of [2]catenane **12** was confirmed by mass spectrometry (fragmentation and MS–MS studies) and <sup>1</sup>H NMR spectroscopy. The <sup>1</sup>H NMR spectrum of catenane **12** in  $\text{CDCl}_3$  is shown in Figure 5b. The upfield shifts of the signals as compared to macrocycle **11** (Figure 5a) and building block **10** (Figure 5c) show the same general trends found in the heterocircuit catenane produced by the single macrocyclization active template CuAAC reaction, **7** (Figure 3).

## Conclusions

The active template concept developed for rotaxanes can be successfully extended to the more demanding requirements of catenane synthesis. Heterocircuit [2]catenanes were prepared in 21–53% yields through Cu(I)-mediated active template single macrocyclization strategies employing the Cadiot–Chodkiewicz (forming a symmetrical bisacetylene-containing macrocycle) or CuAAC “click” reaction (forming an unsymmetrical triazole-containing macrocycle) and preformed monodentate or bidentate macrocyclic ligands. The CuAAC reaction could also be used to assemble homocircuit [2]catenanes from a single type of acyclic building block in a one-pot procedure in up to 46% yield, a remarkable catalytic assembly reaction notable for its selectivity for the interlocked architecture over noninterlocked macrocyclic products. The application of such strategies to higher order interlocked structures is currently under investigation in our laboratory.

**Acknowledgment.** We thank Juraj Bella for assistance with the high field <sup>13</sup>C NMR studies and Syngenta for a Ph.D. studentship (to P.R.M.). D.A.L. is an EPSRC Senior Research Fellow and holds a Royal Society–Wolfson research merit award.

**Supporting Information Available:** Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA9070317

# En Route to a Molecular Sheaf: Active Metal Template Synthesis of a [3]Rotaxane with Two Axles Threaded through One Ring

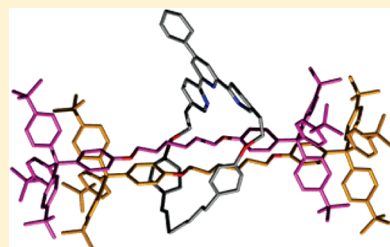
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 Supporting Information

**ABSTRACT:** We report that a 2,2':6',2''-terpyridylmacrocycle–Ni complex can efficiently mediate the threading of two alkyl chains with bulky end groups in an active metal template  $\text{sp}^3$ -carbon-to- $\text{sp}^3$ -carbon homocoupling reaction, resulting in a rare example of a doubly threaded [3]rotaxane in up to 51% yield. The unusual architecture is confirmed by X-ray crystallography (the first time that a one-ring-two-thread [3]rotaxane has been characterized in the solid state) and is found to be stable with respect to dethreading despite the large ring size of the macrocycle. Through such active template reactions, in principle, a macrocycle should be able to assemble as many axles in its cavity as the size of the ring and the stoppers will allow. A general method for threading multiple axles through a macrocycle adds significantly to the tools available for the synthesis of different types of rotaxane architectures.



## INTRODUCTION

Rapid advances in many aspects of template synthesis, ligand design, and methods for covalent capture are allowing access to increasingly complex mechanically interlocked architectures.<sup>1</sup> However, while there are numerous examples of rotaxanes consisting of several rings threaded onto a single axle,<sup>2,3</sup> rotaxanes featuring multiple axles passing through a single ring remain rare.<sup>4–6</sup> This disparity is accounted for by the relative structural demands on the cyclic component(s) and thread(s). The structural elements used for the synthesis of a [2]rotaxane can, in principle, be extrapolated to multiring rotaxanes with relative ease by simply employing an elongated axle with several template sites without changing the size and nature of the macrocycle or stoppers.<sup>2</sup> The synthesis of multithread rotaxanes is more challenging: The ring may require more than one template site to assemble multiple threads (using traditional template methods), and must be considerably larger than required for a [2]rotaxane in order to accommodate more than one axle, an issue that is further complicated by the sheer size of the stoppers required to prevent dethreading of large macrocycles.<sup>4b,c,e,7</sup> Furthermore, the macrocycle–thread interactions that direct the assembly of the interlocked components must overcome the sometimes severe steric clashes that can occur between crowded thread units.

Active metal template synthesis<sup>8</sup> is a strategy for the construction of mechanically interlocked architectures in which a macrocycle-bound transition metal ion acts as both the template to entwine or thread the components and as a catalyst to promote the covalent bond forming reaction that captures the interlocked structure. Unlike traditional 'passive' metal template approaches to the synthesis of rotaxanes,<sup>9</sup> a permanent metal binding site is only required on the macrocycle—the thread component may

have little<sup>8a–e,g,k,m</sup> or no<sup>8n</sup> binding affinity for the transition metal ion after rotaxane formation. Thus, the metal ion may be able to turn over during the reaction, a corollary being that in some cases only a substoichiometric amount of the metal is required to achieve the transformation.<sup>8a,c–e,k</sup> Here, we report on a further consequence of employing such a catalytic template system: a single active template site in a suitably large macrocycle is able to mediate the sequential formation of two threads through one ring, giving rise to a doubly threaded [3]rotaxane. To do so the cavity of the macrocycle must be large enough to accommodate two axles yet still small enough to prevent dethreading. A 35-membered ring with an endotopic 2,2':6',2''-terpyridine (terpy) binding site successfully promotes one-ring-two-threads [3]rotaxane formation via an active template Ni-catalyzed homocoupling of alkyl bromides terminated with tris(*t*-butylphenyl)methyl groups in up to 51% yield in a simple one-pot reaction.

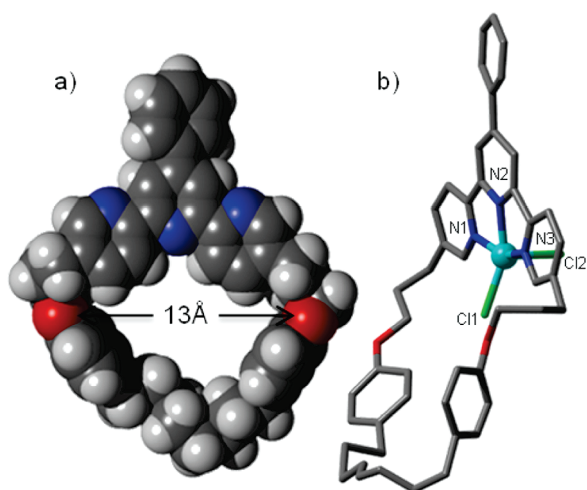
## RESULTS AND DISCUSSION

We recently reported the discovery of a Ni-catalyzed  $\text{sp}^3$ -carbon-to- $\text{sp}^3$ -carbon alkyl bromide homocoupling reaction and its application to the active metal template synthesis of [2]-rotaxanes.<sup>8n</sup> An essential feature of the reaction is the use of a tridentate nitrogen-donor-atom ligand to inhibit competing  $\beta$ -hydride elimination of alkyl-Ni intermediates during the Ni-catalyzed reductive dimerization. [2]Rotaxane formation was demonstrated using a macrocyclic pyridine-2,6-bisoxazoline ligand. However, the bisoxazoline macrocycle and rotaxane were

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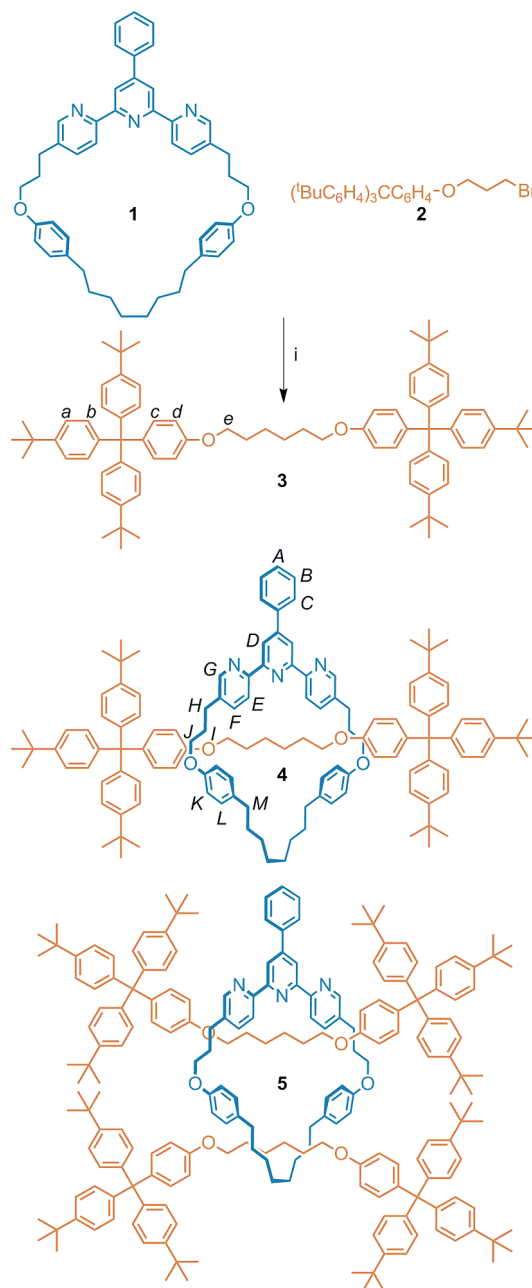
**Figure 1.** X-ray crystal structure of (a) macrocycle **1**, from a single crystal obtained by vapor diffusion of diethyl ether into a chloroform solution, space filling representation, and (b) complex **1**·NiCl<sub>2</sub>, from a single crystal obtained by slow diffusion of methanol into a chloroform solution, stick representation. Solvent molecules and hydrogen atoms of **1**·NiCl<sub>2</sub> are omitted for clarity. Nitrogen atoms are shown in blue, oxygen atoms red, chlorine atoms green, nickel atoms cyan (ball), hydrogen atoms white, and carbon atoms gray. Selected bond lengths [Å] and angles [°]: N1–Ni 2.11, N2–Ni 1.97, N3–Ni 2.12, Cl1–Ni 2.27, Cl2–Ni 2.30, N1–Ni–N2 77.1, N1–Ni–N3 153.5, N2–Ni–Cl1 154.0, Cl1–Ni–Cl2 108.0, N2–Ni–Cl2 98.0.

prone to decomposition, limiting the scope of the reaction. Optimization of the Ni-catalyzed dimerization protocol with commercially available substrates revealed that terpy groups are also suitable catalyst ligands for this transformation and are much more stable than oxazoline units.<sup>8n,10</sup> It appeared that integration of the robust terpy binding motif into a macrocycle might overcome the rotaxane stability issue, enabling the Ni-catalyzed alkyl bromide homocoupling reaction to be rather more synthetically useful.

Macrocycle **1** was synthesized from commercially available 2,5-dibromopyridine and 4-(4-methoxyphenyl)-butyl bromide in 24% overall yield, with 8 steps in the longest linear sequence (for details of the synthesis, see the Supporting Information). Substitution at the 5- and 5''- position of the terpy ring system allows rotation of the pyridyl rings relative to one another<sup>11</sup> upon chelation of Ni<sup>II</sup> and the 120° turn angle of the rigid aromatic framework induces cavity dimensions appropriate for use in rotaxane-forming reactions. Single crystals of both macrocycle **1** and the corresponding complex **1**·NiCl<sub>2</sub> were obtained by slow vapor diffusion of diethyl ether or methanol into chloroform solutions and the solid state structures determined by X-ray crystallography (Figure 1). The crystal structure of **1** shows that the rigid terpy portion of the macrocycle generates an aperture with a cavity width of up to 13 Å (Figure 1a). The terpyridyl ring system switches to a cis–cis geometry upon coordination to Ni<sup>II</sup> (Figure 1b), holding the metal center endotopically as required for a rotaxane-forming active template mechanism.

The catalytically active macrocycle–Ni<sup>0</sup> complex was formed *in situ* by stirring **1** with NiCl<sub>2</sub>·6H<sub>2</sub>O in *N*-methyl-2-pyrrolidone (NMP) followed by reduction with Zn powder. After addition of a solution of the ‘stoppered’ alkyl bromide **2** in tetrahydrofuran (THF), the reaction mixture was heated at 60 °C for 18 h (Scheme 1 and Table 1), then demetalated with a basic

**Scheme 1.** Synthesis of [2]- and [3]Rotaxanes via a Nickel-Catalyzed Active Template Reductive Homocoupling Reaction<sup>a</sup>



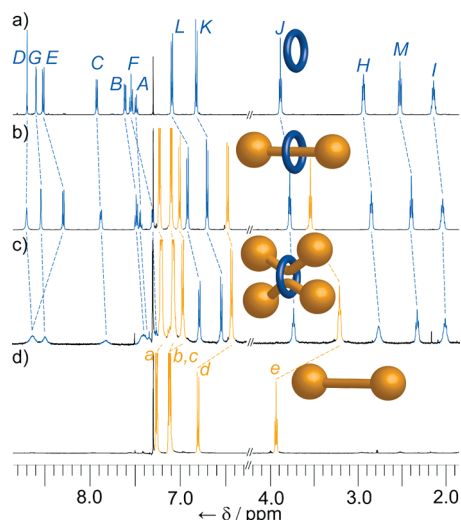
<sup>a</sup> Reagents and conditions: (i) 1. NiCl<sub>2</sub>·6H<sub>2</sub>O, Zn, NMP-THF (1:1), 60 °C, 18 h. 2. Na<sub>2</sub>EDTA-NH<sub>3</sub>(aq).

ethylenediaminetetraacetic acid disodium salt–ammonia (Na<sub>2</sub>EDTA-NH<sub>3</sub>) solution.<sup>12</sup> Pleasingly, a stoichiometric amount of stoppered bromide **2** led to complete conversion to homocoupled products and formation of the desired [2]rotaxane **4** as observed by analysis of the crude reaction mixture by <sup>1</sup>H NMR spectroscopy and mass spectrometry. Purification of the crude reaction mixture by size-exclusion chromatography revealed only a modest 14% yield of [2]rotaxane **4** (Table 1, entry 1). However, as the catalytic Ni complex can turn over during the reaction, the yield of [2]rotaxane could be increased to 48% by employing a

**Table 1. Conversion of Macrocycle 1 to [2]Rotaxane 4 and [3]Rotaxane 5 (Scheme 1)**

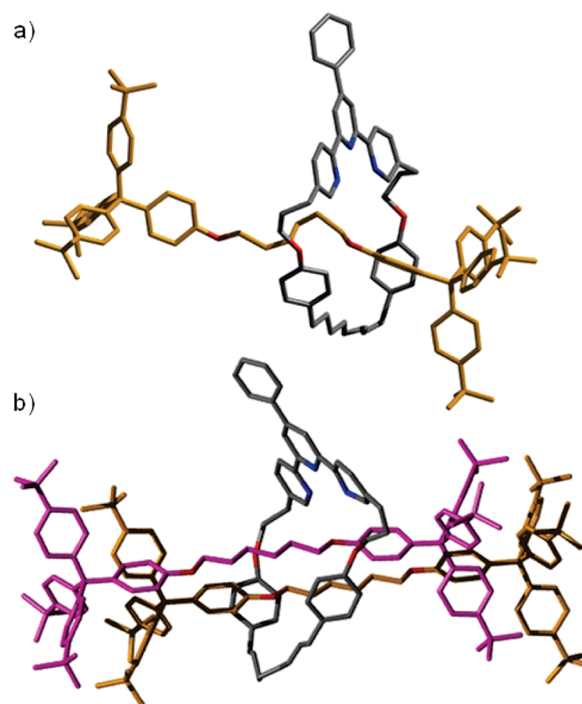
entry	equiv 2	[2]rotaxane 4 yield <sup>a</sup>	[3]rotaxane 5 yield <sup>a</sup>
1 <sup>b</sup>	2.0	14%	4%
2 <sup>b</sup>	5.0	48%	9%
3 <sup>b</sup>	10.0	29%	30%
4 <sup>c</sup>	20.0	20%	51%

<sup>a</sup> Isolated yields based on macrocycle 1. <sup>b</sup> Ten equivalents of Zn. <sup>c</sup> Fifteen equivalents of Zn. In all cases,  $\geq 95\%$  conversion to homocoupled products was determined by <sup>1</sup>H NMR analysis of the crude reaction mixture.<sup>12</sup>



**Figure 2.** Partial <sup>1</sup>H NMR spectra (500 MHz, CDCl<sub>3</sub>, 298 K) of (a) macrocycle 1, (b) [2]rotaxane 4, (c) [3]rotaxane 5, and (d) non-interlocked thread 3. The lettering corresponds to that shown in Scheme 1.

2.5-fold excess of bromide 2 (Table 1, entry 2). To our surprise, when a 5-fold excess of bromide 2 was used in an attempt to further increase the amount of 4 formed, the isolated yield of [2]rotaxane fell to 29% (Table 1, entry 3). The reason behind this unexpected drop in yield of 4 became apparent during the size-exclusion purification procedure: a substantial amount of material eluted before the [2]rotaxane indicating another product with a larger hydrodynamic volume. <sup>1</sup>H NMR spectroscopy and mass spectrometry revealed that the second product was the one-ring-two-thread [3]rotaxane 5 (Scheme 1).<sup>13</sup> Repetition of the reaction protocol using less equivalents of 2 (Table 1, entries 1 and 2) confirmed small amounts (<10%) of 5 are also formed under those conditions. The [3]rotaxane proved to be the major product when using a 10-fold excess of bromide 2, producing a total of 71% interlocked products of which 51% was [3]rotaxane 5 (Table 1, entry 4). As complete conversion of 2 occurred and unconsumed macrocycle 1 could be recovered, the yield of interlocked products reflects the proportion of intermediate dialkyl-Ni species that react with the axle precursors protruding from opposite faces of the macrocycle (leading to rotaxane 4 or 5) or from the same face (leading to the non-interlocked axle 3). Unlike the bisoxazoline-macrocycle rotaxanes previously prepared using the Ni-catalyzed active metal template sp<sup>3</sup>-carbon-to-sp<sup>3</sup>-carbon homocoupling reaction,<sup>8n</sup> the terpy-macrocycle-based [2]rotaxane 4 and [3]rotaxane 5 proved completely stable (no degradation observed over several months, vide infra).

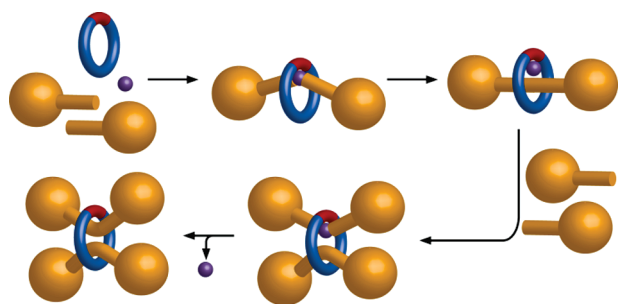


**Figure 3.** X-ray crystal structures of (a) [2]rotaxane 4, and (b) [3]rotaxane 5, from single crystals obtained by slow diffusion of methanol into deuteriochloroform solutions. Hydrogen atoms and solvent molecules are omitted for clarity. Nitrogen atoms are shown in blue; oxygen atoms red; and the carbon atoms of the different components in gray, gold, and pink.

Comparison of the <sup>1</sup>H NMR spectrum (500 MHz, CDCl<sub>3</sub>, 298 K) of the [2]rotaxane 4 (Figure 2b) with those of its non-interlocked components (macrocycle 1 and thread 3; Figure 2, panels a and d, respectively) shows upfield shifts of protons from the thread and macrocycle typical of regions of mechanically interlocked structures that spend some time face-on to aromatic rings. The uniform distribution of the modest shielding effects suggest that no particular co-conformation is stabilized—the macrocycle and thread can undergo relatively unrestricted motion relative to one another, as would be expected in a system with no strong intercomponent interactions. However, threading of a second alkyl chain axle through the ring ([3]rotaxane 5, Figure 2c) results in increased shielding of most of the thread protons as they are forced to spend more time closer to the aromatic rings of the macrocycle. Several of the macrocycle resonances (H<sub>A–H</sub>) are broadened, possibly as a consequence of the steric congestion between the chains causing some co-conformational exchange processes, such as macrocycle pirouetting, to slow to rates close to the <sup>1</sup>H NMR time scale.

Single crystals of 4 and 5 suitable for X-ray diffraction were grown by slow diffusion of methanol into solutions of each rotaxane in deuterated chloroform. The crystal structures (Figure 3) confirm the constitution of both rotaxanes and the doubly threaded nature of [3]rotaxane 5—the first time a one-ring-two-thread [3]rotaxane structure has been determined in the solid state. In the solid state, the alkyl chain of the thread of [2]rotaxane 4 (Figure 3a) adopts a folded conformation where it passes through the ring (C–C–C–C dihedral angles  $50^\circ \leq \phi \leq 160^\circ$ ), apparently to occupy as much of the space within the macrocyclic cavity as possible, driven by crystal packing forces. In





**Figure 4.** Active metal template synthesis of [3]rotaxanes. A macrocyclic ligand (blue) with an endotopic binding site (red) coordinates to a metal ion (purple). The metal can mediate the construction of interlocked products by promoting the formation of covalent bonds through the cavity. If the ring is large enough to accommodate two threads and the catalytic metal center can turn over, a doubly threaded [3]rotaxane can be assembled in a simple one-pot procedure.

contrast, both alkyl chains of [3]rotaxane **5** adopt fully extended zigzag conformations ( $C-C-C$  dihedral angles  $\phi \approx 180^\circ$ )—there is comparatively little unfilled space remaining in the cavity of the doubly threaded macrocycle—and are offset from one another by approximately 4.5 Å along the vector of the thread which minimizes steric clashes between the bulky trityl stoppers. Avoiding stopper–stopper repulsion, perhaps through the use of longer threads, may be an important factor for extrapolating this methodology to the preparation of rotaxanes in which more than two axes are threaded through a single ring, particularly as the stopper size required to prevent dethreading increases dramatically with only small increases in macrocycle size.<sup>4b,c,e,7</sup>

The formation of [3]rotaxane **5** likely proceeds in a stepwise manner via a [2]rotaxane intermediate as depicted schematically in Figure 4. After active template assembly of the first axle (to give [2]rotaxane **4**), the catalytically active metal center is regenerated and can then gather another pair of building blocks and mediate the formation of a second covalent bond, furnishing the [3]rotaxane. Other active template reactions may also have the potential to form multiply threaded rotaxanes. However, the macrocycles used in previous studies have not possessed a cavity of a size capable of accommodating more than one thread and a metal ion simultaneously.<sup>8</sup>

The paucity of doubly threaded rotaxanes in the literature<sup>4</sup> stems from the delicate balance that must be struck between the relative dimensions of the components in order to successfully entrap two axes in one ring—the macrocycle must possess a cavity large enough to accommodate both threads but should not be so large as to be able to slip over the stoppering groups. Indeed, in previously reported syntheses of doubly threaded [3]rotaxanes around an octahedral metal template<sup>4c</sup> or using DNA building blocks,<sup>4e</sup> removal of the template interaction results in metastable structures that dethread over several hours or days at ambient temperature, illustrating the general trade-off between synthetic accessibility and stability for such structures. Neither [2]rotaxane **4** nor [3]rotaxane **5** showed any signs of dethreading over several months at ambient temperature or upon heating for several hours at 60 °C (see the Supporting Information). As [2]rotaxane **4** is stable, isolable, and can be obtained in good yield (up to 48%; Table 1, entry 2), it may be useful as an intermediate for the synthesis of [3]rotaxanes with two constitutionally different threads,<sup>4a,e</sup> ring-in-ring complexes<sup>14</sup>

and for the stepwise assembly of more complex interlocked architectures, such as heterocircuit Borromean rings.

## CONCLUSIONS

2,2':6',2''-Terpyridyl macrocycle **1** is a highly effective ligand for the Ni-catalyzed active template  $sp^3$ -carbon-to- $sp^3$ -carbon homocoupling of alkyl bromides to form chemically robust and kinetically stable rotaxanes. The axes of the rotaxanes are simple alkyl chains (terminated with suitably bulky groups to prevent dethreading) rendering the synthesis effectively traceless in terms of the structure of the threads. The cavity of the 35-membered ring of **1** is sufficiently small that tris(*t*-butylphenyl)-methyl groups can act as the stoppers, but large enough that two alkyl chain threads can be accommodated within the cavity. A one-ring-two-thread [3]rotaxane **5** was isolated in up to 51% yield in a simple one-pot procedure from a five component reaction that features two mechanical bond-forming steps. A small increase in macrocycle size may enable higher order multiply threaded rotaxanes to be synthesized, for example, a ring clasping three threads in its cavity, a type of molecular architecture for which no examples exist to date. Ways of using this, presently unique, synthetic tool for assembling sheaves<sup>15</sup> of molecular chains with no recognition elements<sup>6</sup> are currently being investigated in our laboratory.

## ASSOCIATED CONTENT

**S Supporting Information.** Experimental procedures and spectral data for all compounds and the details of the X-ray analyses of **1**, **1**·NiCl<sub>2</sub>, **4**, and **5** including cif files. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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the reactants to be in solution at the start of the reaction. Heating to 60 °C was necessary to allow reactions with >5 equiv of **2** to reach completion within 18 h. The proportion of interlocked and non-interlocked products was unchanged when the reactions were carried out with DMF as solvent and/or at room temperature (other conditions as for Table 1, entry 2).

(13) Two-ring-one-thread [3]rotaxanes have previously been observed as byproducts in Cu-catalyzed azide-alkyne cycloaddition (CuAAC) active metal template reactions, see ref 8d.

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(15) A “sheaf” (plural: sheaves) is a bundle of objects held together by a band or other mechanical binder. Familiar examples include the way that wheat, rye, and other cereals are traditionally bound with straw or twine after reaping.



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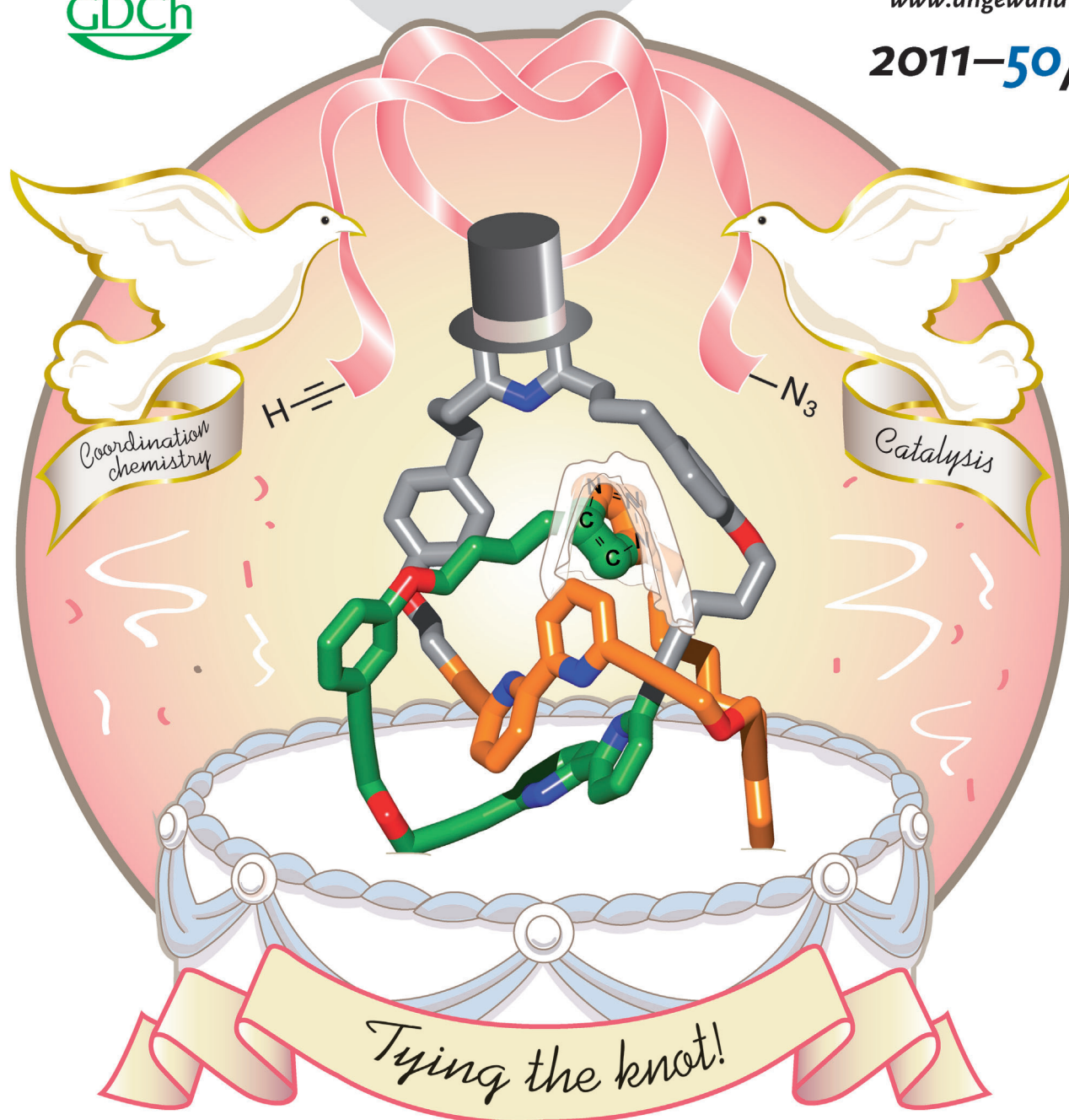
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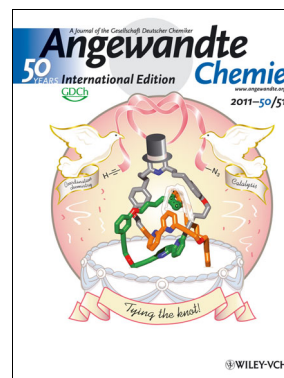
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## Back Cover

**Perdita E. Barran, Harriet L. Cole, Stephen M. Goldup,  
David A. Leigh,\* Paul R. McGonigal, Mark D. Symes, Jhenyi Wu, and  
Michael Zengerle**

**The marriage** of coordination chemistry and catalysis enables metal ions to work in partnership in the active-template synthesis of the smallest molecular trefoil knot reported to date. In their Communication on page 12280 ff., D. A. Leigh et al. describe how one copper(I) ion entangles an acyclic building block to create a loop in the ligand whilst a second copper(I) ion gathers the ligand's reactive end groups, threads the loop, and catalyzes the covalent capture of the 76-atom knot by an alkyne–azide “click” reaction.



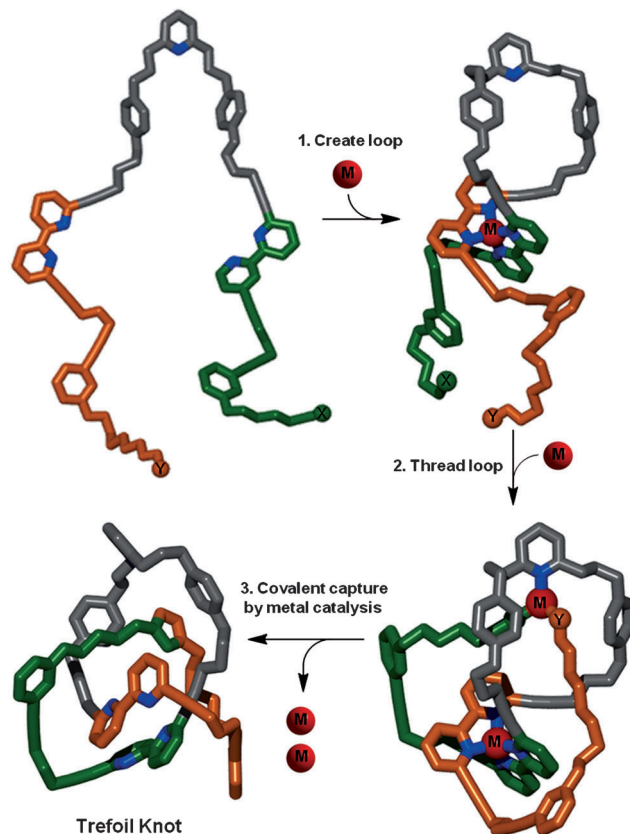
## Active-Metal Template Synthesis of a Molecular Trefoil Knot\*\*

Perdita E. Barran, Harriet L. Cole, Stephen M. Goldup, David A. Leigh,\* Paul R. McGonigal, Mark D. Symes, Jhenyi Wu, and Michael Zengerle

Although many different approaches to catenanes and rotaxanes have been introduced,<sup>[1]</sup> few strategies have been successfully developed for the synthesis of molecular knots.<sup>[2]</sup> Trefoil knots, the simplest prime knot other than the topologically trivial unknot (i.e., any ring or simple macrocycle),<sup>[3]</sup> have been found in DNA,<sup>[4]</sup> proteins,<sup>[5]</sup> and in synthetic polymers.<sup>[6]</sup> Sauvage and co-workers prepared the first synthetic molecular knot by using the preorganization of two ligand strands around two tetrahedral Cu<sup>I</sup> centers as the key template interaction to generate the three crossing points required for a trefoil knot.<sup>[7]</sup> Subsequently, donor–acceptor interactions,<sup>[8]</sup> Watson–Crick base pairing,<sup>[9]</sup> amide hydrogen bonding,<sup>[10]</sup> and ligand folding around an octahedral metal ion<sup>[11]</sup> have all been used to template the formation of molecular trefoil knots.<sup>[12]</sup>

A few years ago a strategy for the synthesis of rotaxanes and catenanes was introduced in which metal ions play a dual role, acting as a template to entwine or thread the building blocks while also actively catalyzing the bond-forming reaction that covalently traps the interlocked structure.<sup>[13]</sup> This “active-template” approach has proven to be an effective route to various types of mechanically interlocked molecules and can be applied by using an increasing number of different transition-metal-catalyzed reactions.<sup>[13]</sup> Herein we report an active-template reaction that occurs through a loop generated through classical “passive-template” coordination to synthesize the smallest trefoil knot reported to date. The trefoil knot was characterized by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy, mass spectrometry, and by drift tube ion mobility mass spectrometry (DT IM-MS) experiments that show that the molecular knot has a significantly smaller cross-sectional area (with a narrower distribution) than the corresponding open-chain and unknot-macrocycle isomers.

To apply active-template synthesis to a trefoil knot architecture, we envisaged a system (Figure 1) in which a single molecular strand with reactive functional groups at each terminus (X and Y) could be geometrically manipulated and knotted through multiple interactions with metal ions



**Figure 1.** Schematic representation of the active-template synthesis of a molecular trefoil knot. A single-strand ligand with one monodentate and two bidentate binding sites (blue) and two functional end groups (X and Y) is knotted by the action of metal ions (red, M). Step 1: One metal ion creates a loop by coordination to the bidentate binding sites. Step 2: The other metal ion binds to the functional end groups and, through its preferred coordination geometry, threads the loop. Step 3: The knotted architecture is captured by metal-catalyzed covalent bond formation between X and Y.

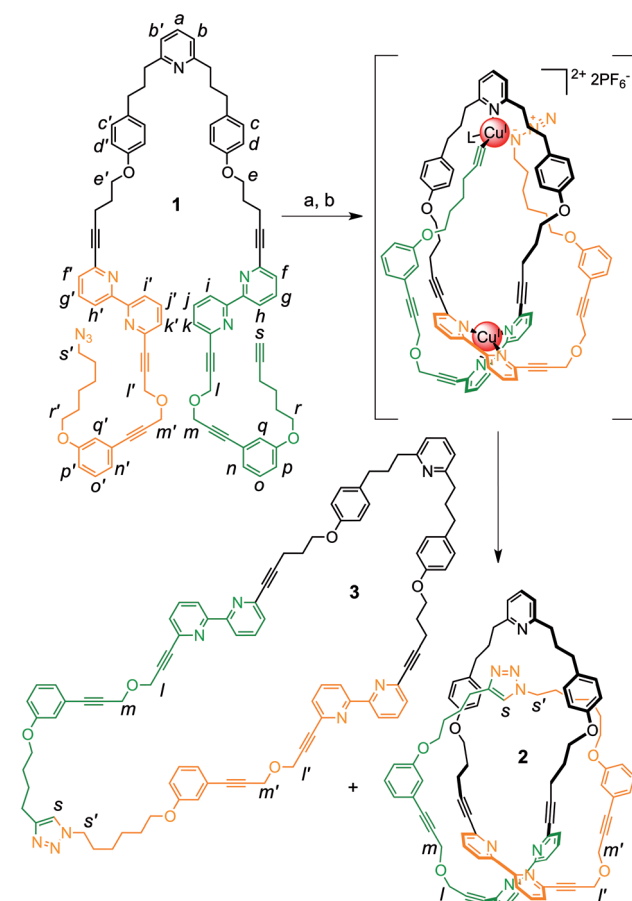
(M). First, a loop in the strand would be formed by coordination of two bidentate binding sites in the strand to a tetrahedral metal ion (Figure 1, step 1). A second metal ion, bound endotopically within the loop by a monodentate ligating site, would then perform the twofold tasks of 1) gathering both functional end groups in a specific orientation that is dictated by the metal's preferred coordination geometry and places them on opposite sides of the loop (Figure 1, step 2), and 2) catalyzing a covalent-bond-forming reaction between the end groups to generate the molecular trefoil knot (Figure 1, step 3).

Ligand **1** (Scheme 1) was synthesized in nine steps from commercially available starting materials (for experimental

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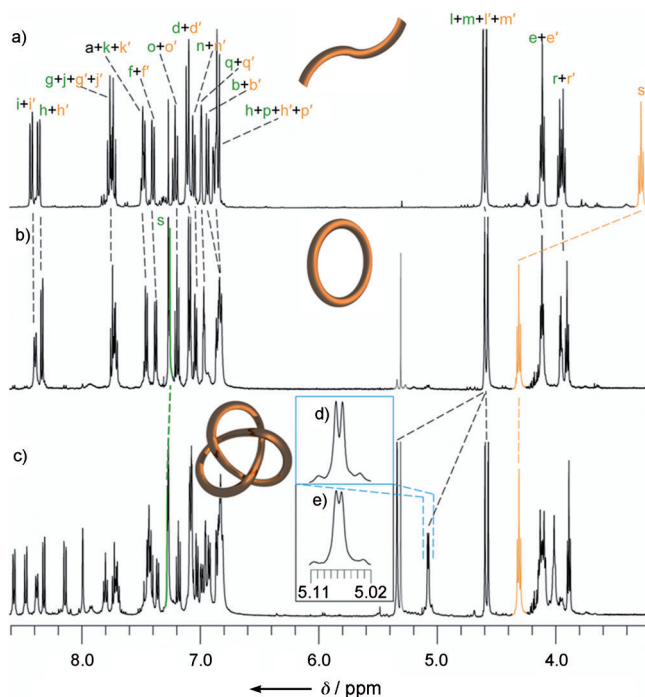
**Scheme 1.** Active-metal-template synthesis of trefoil knot **2**: a)  $\text{CHCl}_3/\text{CH}_3\text{NO}_2$  (4:1),  $[(\text{CH}_3\text{CN})_4\text{Cu}]\text{PF}_6$  (1.5 mol per mol of **1**),  $60^\circ\text{C}$ , 96 h; b)  $\text{Na}_2\text{EDTA}$ ,  $\text{NH}_3$ , **2** 24%, **3** 10%. Trefoil knots are topologically chiral;<sup>[2,3]</sup> only one enantiomer of **2** is shown.

details see the Supporting Information). The single-strand molecule has three potential metal binding sites: two bipyridyl groups to create the loop (and one of the three required crossing points) by chelation to a tetrahedral  $\text{Cu}^{\text{I}}$  ion, and a 2,6-pyridine unit to bind the catalytically active metal center. The  $\text{Cu}^{\text{I}}$ -catalyzed azide–alkyne cycloaddition<sup>[14]</sup> (CuAAC) “click” reaction was chosen for the covalent-capture reaction that forms the remaining two crossing points, as it utilizes  $\text{Cu}^{\text{I}}$  ions (thus avoiding the complication of having different types of metal ions in the reaction) and because previous studies have shown this reaction to be highly effective in rotaxane- and catenane-forming active-template reactions.<sup>[13a,d,i,k,n,15]</sup> Molecular modeling<sup>[16]</sup> was used to estimate an appropriate length for the alkyl chain spacers between the functional end groups and the  $\text{Cu}^{\text{I}}$  binding sites.

We initially investigated reaction conditions for the active-metal-template knotting reaction of ligand **1** (Scheme 1) using dichloromethane, chloroform, and 1,2-dichloroethane, as these solvents had been employed in previously reported CuAAC active-template reactions.<sup>[13a,d,i,k,n]</sup> However, upon addition of  $[(\text{Cu}(\text{CH}_3\text{CN})_4)\text{PF}_6]$  to a dilute solution of **1** in any of these halogenated solvents, a precipitate formed immediately.<sup>[17]</sup> After screening a number of solvent mixtures,

4:1 chloroform–nitromethane was found to maintain the reactants and products in solution during the course of the reaction. An optimized concentration (1.5 mM) of **1**, with 1.5 molar equivalents<sup>[18]</sup> of  $[(\text{Cu}(\text{CH}_3\text{CN})_4)\text{PF}_6]$  at  $60^\circ\text{C}$ , led to complete consumption of **1** after 4 days, as evidenced by the  $^1\text{H}$  NMR spectrum of the crude reaction mixture.

After demetalation by washing with a basic ethylenediaminetetraacetic acid disodium salt/ammonia ( $\text{Na}_2\text{EDTA}\cdot\text{NH}_3$ ) solution,<sup>[13g]</sup> the products were purified using a combination of size-exclusion (SEC) and high-performance liquid (HPLC) chromatographies. SEC enabled facile removal of the oligomeric by-products and the resulting mixture was separated into its individual components by reverse-phase preparative HPLC. Two products were isolated, in 24% and 10% yields, both of which were shown to be isomers of the acyclic starting material **1** by high-resolution electrospray ionization–mass spectrometry (HRESI-MS; see Figure 2 caption and the Supporting Information). The isomer formed in lower yield (10%) was identified as the simple macrocycle **3** (i.e., a cyclic structure with unknot topology) by comparison of its  $^1\text{H}$  NMR spectrum (Figure 2b) with that of the starting

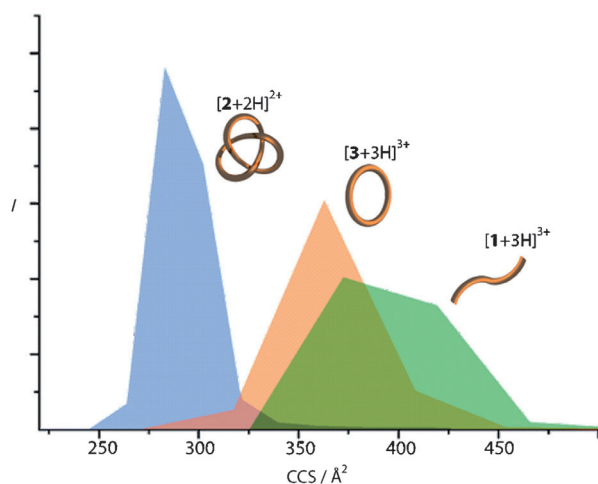


**Figure 2.** Partial  $^1\text{H}$  NMR spectra (400 MHz,  $\text{CDCl}_3$ , 300 K) of three isomers (**1**, **2**, and **3**) of molecular formula  $\text{C}_{88}\text{H}_{84}\text{N}_8\text{O}_6$ : building block (**1**) and the two products (**2** and **3**) isolated from the reaction of **1** shown in Scheme 1. The signals of the  $\text{H}_{\text{s}}$  protons, associated with the  $-\text{NCH}_2-$  group (adjacent to the azide in **1** and the triazole ring in **2** and **3**), are shown in orange. The signals of the  $\text{H}_{\text{g}}$  protons, associated with the  $-\text{CH}-$  of the triazole ring in **2** and **3**, are shown in green. a) Open-chain building block **1**, HRESI-MS:  $m/z$  1361.6613  $[\text{M}+\text{H}]^+$  (calcd for  $\text{C}_{88}\text{H}_{85}\text{N}_8\text{O}_6$  1361.6597). b) Unknot-macrocycle **3**, HRESI-MS:  $m/z$  1361.6603  $[\text{M}+\text{H}]^+$ . c) Trefoil knot **2**, HRESI-MS:  $m/z$  1361.6601  $[\text{M}+\text{H}]^+$ . Expansion of the region between  $\delta = 5.11$  and  $5.02$  ppm of the d) 500 MHz and e) 400 MHz  $^1\text{H}$  NMR spectra of **2** showing a propargylic methylene ( $\text{H}_{\text{l,l',m,or,m'}}$ ) AB system ( $J_{\text{AB}} = 13.2$  Hz). The protons are diastereotopic as a consequence of the chirality of the trefoil knot. The lettering corresponds to that shown in Scheme 1.



material **1** (Figure 2a). The spectrum of the flexible 76-membered-ring macrocycle (**3**) is very similar to that of the open-chain isomer (**1**), the only significant differences being the shift of the  $H_s$  ( $-NCH_2-$ ) and  $H_a$  protons (the latter from  $\delta = 2.0$  ppm in **1** to  $\delta = 7.25$  ppm in **3**) following conversion of the azide and terminal alkyne to the triazole ring.

The isomer isolated in greater yield (24 %) was confirmed as the trefoil knot **2** through a series of NMR, mass spectrometry, and DT IM-MS experiments. The  $^1H$  NMR spectrum of **2** (Figure 2c) is very different to those of its open-chain **1** and unknot-macrocycle **3** isomers (Figure 2a and b). Many of the resonances in the aromatic region of **2** are separated into two sets of inequivalent signals. The increase in the overall number of resonances observed is a result of the loss of the pseudosymmetry of **1** (and **3**) upon formation of the conformationally contorted trefoil knot structure—the 76-atom entwined loop is the smallest knot reported to date<sup>[11c]</sup>—and molecular modeling<sup>[16]</sup> and DT IM-MS results (see below) indicate it to be tightly wound. Two of the propargylic methylene resonances (two of  $H_{l/m/m'}$ ) are shifted significantly downfield in **2** compared to the unknot-macrocycle **3** (from  $\delta = 4.59$  ppm to  $\delta = 5.33$  and 5.07 ppm). It appears that these protons spend a significant amount of time edge-on to an aromatic ring in low-energy conformations of the knot, and are deshielded through ring current effects. Notably, the propargylic methylene resonance at  $\delta = 5.07$  ppm appears as an AB system (Figure 3d,e), thus indicating that the protons are diastereotopic.<sup>[19]</sup> This behavior is a consequence of the inherent chirality of a trefoil knot.<sup>[11d,20]</sup>



**Figure 3.** DT IM-MS spectra of building block **1** (green,  $[M+3H]^{3+}$ ), and products **2** (blue,  $[M+2H]^{2+}$ ) and **3** (orange,  $[M+3H]^{3+}$ ) isolated from the reaction of **1** shown in Scheme 1. The CCS area distributions were calculated from the measured arrival times for the highest observed charge state of each isomer. Data shows the arrival times at a drift voltage of 50 V. Intensities ( $I$ ) are normalized to the peak areas. Ligand strand **1**, which is expected to have a large degree of flexibility, exhibits the broadest distribution and largest CCS. Unknot-macrocycle **3** has a smaller CCS and narrower distribution and trefoil knot **2** displays the smallest CCS and the narrowest distribution, reflecting its compact structure and persistent size and shape.

Further insight into the structure of trefoil knot **2** was provided by drift tube ion mobility mass spectrometry (DT IM-MS). In these experiments, the velocity with which an ion travels through a cell containing a buffer gas (commonly helium), under the influence of a weak electric field, depends on the collision cross section (CCS) of the ion with the buffer gas (averaged over all possible orientations of the ion).<sup>[21,22]</sup> A larger ion with few conformational restrictions takes longer to traverse the drift cell, undergoing more collisions with the buffer gas, than a smaller, more compact, structure. This behavior has previously been demonstrated for naturally occurring antimicrobial peptides<sup>[21]</sup> and for synthetic cyclic and linear peptides.<sup>[22]</sup> With low charge numbers, flexible molecules may wrap tightly around the charged regions in order to solvate them with heteroatoms and aromatic rings. However, as the number of charges on a molecular ion increases, the size of the adopted conformations increases as electrostatic repulsions try to force the largest distance between the charges that the molecule will allow. In general, the observed CCS increases with the amount of charge that a flexible structure carries. In addition to the magnitude of the CCS, which gives information about the size of the molecular ion, the broadness of the distribution indicates the flexibility (the number of differently sized and shaped conformations adopted) of the molecular structure.

Following nanoelectrospray ionization, DT IM-MS showed significant differences in the rotationally averaged CCS areas of ions of the three isomers **1–3** (Figure 3).<sup>[23]</sup> The largest average CCS areas of the open-chain isomer **1** ( $[1+3H]^{3+}$  ion) and unknot-macrocycle **3** ( $[3+3H]^{3+}$  ion) were  $(395 \pm 3.5) \text{ \AA}^2$  and  $(368 \pm 5.3) \text{ \AA}^2$ , respectively. The largest average CCS area observed for the trefoil knot **2** ( $[2+2H]^{2+}$  ion) was  $(292 \pm 1) \text{ \AA}^2$ . Therefore for the highest charge state observed for each species, open-chain isomer **1** has a larger molecular cross-section than unknot-macrocycle **3** which, in turn, has a much larger cross-sectional area than trefoil knot **2**. Furthermore, the open-chain isomer **1** has the broadest CCS distribution, followed by the unknot-macrocycle **3**, with the trefoil knot **2** having the narrowest range. These results indicate that the trefoil knot has a much more compact and inflexible structure than the unknot-macrocycle, which is more compact and less flexible than the acyclic strand. Calculations of the expected CCS values from the Spartan-minimized<sup>[16]</sup> structures of the most extended form of each molecular species support the observed experimental trend (see the Supporting Information).

In conclusion, we have demonstrated an active-template approach to the synthesis of molecular knots based upon the cooperative manipulation of a ligand with reactive end groups by two metal ions. One of the metal centers creates a loop in the ligand whilst the other catalyzes a covalent-bond-forming reaction that links the end groups through the cavity. The resulting trefoil knot and its unknot and acyclic isomers were characterized by NMR spectroscopy, mass spectrometry, and DT IM-MS experiments. The latter technique is able to discriminate between the isomers through both the size and relative flexibility of their multiply charged molecular ions. Active-template strategies for entangling molecular chains, and novel methods for the structural characterization of the



resulting products,<sup>[24]</sup> may prove useful for the synthesis of other complex molecular structures.

## Experimental Section

**Active-template trefoil knot synthesis:** In a typical procedure, a solution of  $[(\text{CH}_3\text{CN})_4\text{Cu}]\text{PF}_6$  (14.7 mg, 39.4  $\mu\text{mol}$ ) in  $\text{CH}_3\text{NO}_2$  (2.5 mL) was added to a solution of **1** (35.8 mg, 26.3  $\mu\text{mol}$ ) in  $\text{CHCl}_3$  (14 mL) and  $\text{CH}_3\text{NO}_2$  (1.0 mL), and the reaction mixture was heated at 60 °C for 96 h. The solution was allowed to cool to RT and diluted with  $\text{CH}_2\text{Cl}_2$  (30 mL). A 17.5% aqueous solution of  $\text{NH}_3$  saturated with  $\text{Na}_2\text{EDTA}$  (30 mL) was added and the mixture stirred vigorously for 30 min. The phases were separated and the organic phase was further extracted with a 17.5% aqueous solution of  $\text{NH}_3$  saturated with  $\text{Na}_2\text{EDTA}$  (30 mL),  $\text{H}_2\text{O}$  (30 mL), and brine (30 mL), then dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure. The resulting residue was purified by size-exclusion chromatography ( $\text{CH}_2\text{Cl}_2$  mobile phase) followed by preparative HPLC (reverse-phase column, gradient elution: 1) MeOH with 5  $\rightarrow$  0%  $\text{H}_2\text{O}$ , 2) MeOH with 0  $\rightarrow$  10%  $\text{CH}_2\text{Cl}_2$  to give trefoil knot **2** as a colorless film (8.6 mg, 24%) and macrocycle **3** as a yellow film (3.5 mg, 10%). Full details of experimental procedures and compound characterization are given in the Supporting Information.

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- [18] The use of less than a stoichiometric amount of copper is to try to minimize the amount of  $\text{Cu}^{\text{I}}$  ions not coordinated to **1**. “Free”  $\text{Cu}^{\text{I}}$  ions could catalyze the CuAAC reaction without the end groups passing through the ligand strand loop, thus generating unknot macrocycle **3**.  $\text{Cu}^{\text{I}}$  ions can turn over during active-template CuAAC reactions [Ref 13 a,d,i,l] and therefore stoichiometric amounts of the metal are unnecessary.
- [19] The assignment is confirmed as an AB system by a coupling constant value ( $J_{\text{AB}} = 13.2 \text{ Hz}$ ) that is unchanged when measured at 500 MHz (Figure 2d) and 400 MHz (Figure 2e), and  $^1\text{H}$ – $^1\text{H}$  COSY experiments that show that the two protons coupled in the signal are not coupled to other protons in the molecule.
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